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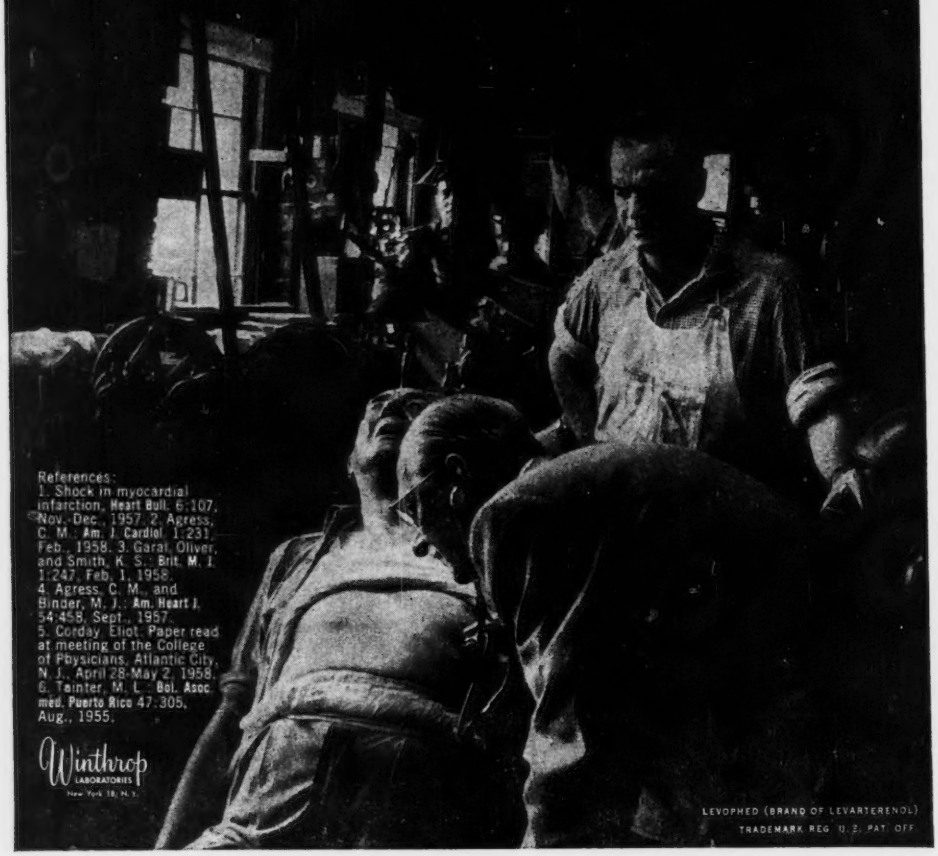

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Editorial

The Unnatural History of (Hypertensive) Disease

THE importance of a thorough familiarity with the natural history of disease is obvious. Through such knowledge one is more likely to recognize the basic processes and better able to anticipate complications and outcome. In addition, examination of the life story of a disorder may provide clues concerning etiology and pathogenesis that sometimes can be transferred to the laboratory for further elucidation. Finally, the evolution of disease must be understood before therapeutic measures can be evaluated with accuracy.

In a strict sense, the epidemiologic approach alone will not provide an understanding of the natural history of disease. The epidemiologist, to be sure, observes, records, and analyzes disease as it occurs under natural conditions among aggregations of individuals. But the perceptive physician requires more than means and averages. He must become aware of the variable course pursued by each patient in the group. Although one man's poison is scarcely another's meat or drink, individual responsiveness varies immensely. The environment, the emotional responses, and "the kind of patient the disease has," as Osler put it, have been known to exert profound influences on the evolution of disease ever since the superb and complete descriptions provided by the Hindu Atreya in pre-Hippocratic days.

From the Department of Medicine, Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, New York, N.Y.

It is not a simple matter to obtain an accurate appraisal of the natural history of a disease. The employment of valid diagnostic criteria is essential. Definitions and terminology which permit acceptable and uniform classification are obligatory. There must be freedom from the stigmata of selection. Sufficient time and funds are required, and few investigators seem to be capable of maintaining the sustained interest and reduced productivity that are concomitant requirements. And, in this day and age, the usual turnpikes traversed by patients have become obscured by a smog of therapies which slows the progress of the ill and hides the view.

Sixty-three years ago Riva-Rocci obliterated the pulse at the wrist by means of the pneumatic cuff. From then until the present time, thousands of articles have appeared in the world literature that deal with blood pressure. Let us examine this printed path with eyes on the road to determine what is known today about the natural history of but one disorder.

Primary hypertension, it is called; no, not even a single name! Essential hypertension, hypertensive vascular disease, or hyperpiesia are synonyms. Some think it is not a unique entity but an assortment of ill-defined illnesses awaiting better definition; others maintain it to be no illness at all—merely an arbitrary setting apart of a group of persons which comprises one extreme of a normal distribution curve. Dozens of experimental methods have been devised to raise the arterial tension, and

the proponents of each method, although they are producing hypertension through secondary mechanisms, note the analogous clinical and pathologic patterns they have achieved.

The diagnosis of primary hypertension seems to be a complicated matter. In fact, in 33 published studies, no less than 14 different diagnostic criteria or combinations thereof have been employed.[1] The disorder is described as being both a common and an uncommon disease, for we find that its prevalence in our population is stated to be from 5 to 25 per cent. Causative and predisposing factors are legion. One reads that heredity, sex, race, constitutional type, personality pattern, psychologic influence, vascular hyperreactivity, physical activity, pregnancy, menopause, occupation, diet, altitude, climate, heavy metal exposure, and so forth, are both all-important and of little significance. The accelerated form, also called malignant hypertension or malignant nephrosclerosis, is either the result of a critical increase in blood pressure, a phenomenon produced by an intensified tempo, or a separate entity associated with, but not the result of, primary hypertension. This form of the illness is discernible on the basis of the diastolic pressure—according to some, on the basis of the symptoms or the development of retinopathy—according to others, or—say the remainder—only retrospectively after an autopsy. Encephalopathy, one complication of the accelerated form of hypertension, may mean dizziness, vomiting, an extreme blood pressure rise, mental symptoms, alterations in the state of consciousness, or a cerebral thrombosis. The answer depends on the ground rules. Even the effect of primary hypertension on survival is open to question, for the mortality reported in different control groups of patients, followed for approximately 10 years, varies from 12 to 91 per cent.

The opinion of this clinic with regard to primary hypertension has been reported elsewhere,[2] but it, too, stems of necessity from criteria and definitions[3] that may or may not be accepted by others.

The message is obvious. It seems unnatural that after all these years there is so little knowledge or agreement concerning the natural history of this and many other common disorders. To the knowledge of this writer, for example, there is no available, adequate study of completely untreated rheumatoid arthritis, and no understanding of the evolution of many common mental diseases. Our obfuscation will increase rather than decrease, as we seek to modify the lives of the ill by means of one therapy or another—and soon there will be no other recourse than to compare treatments, the best of which may, indeed, prove to be more harmful than no treatment.

It is essential that we obtain valid information regarding the natural history of disease. This can be accomplished by a concerted effort to arrive at acceptable diagnostic criteria, by the development of standardized descriptive technics, by the preservation and maintenance of adequate records, and by sufficient effort, time, and funds. This cannot be accomplished without withholding therapy, the value of which has not yet been substantiated by appropriate comparison with the untreated illness.

GEORGE A. PERERA

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Editorial

Symposia

THE primary function of *Circulation* is to serve as a forum for the dissemination of clinical knowledge regarding the cardiovascular system and its related scientific disciplines. The gratifyingly high quality of the original communications attest to the vigor and magnitude of our advancing boundaries. With the advance of our knowledge it is frequently difficult for an investigator to be conversant with the main trends of studies even in neighboring fields and, on the other hand, it is difficult for the clinician to know whether knowledge has reached the stage where it may justifiably and safely be applied to the improvement of diagnosis and treatment of his patient. Thus, a new section, "Clinical Progress," was inaugurated in December 1950 as a monthly feature of *Circulation.*

With increasing specialization and the use of different technics in studying a particular subject, symposia comprising specialists addressing themselves to the same general subject with different technics and points of view have fulfilled an important additional function. In the past, certain symposia have been published from time to time, but beginning with this issue, symposia will form a more regular feature and should prove informative and useful. Beginning with this issue of *Circulation,* "Congestive Heart Failure" will be the subject of 10 articles that will appear in the January, February, and March issues. Other symposia including some presented at the annual scientific meetings will appear in subsequent issues.

HERRMAN L. BLUMGART
Editor-in-Chief

Vesalius

We cannot it is true point to any great physiological discovery as Vesalius' own special handiwork, but in a sense he was the author of discoveries which were made after him. He set before himself a great task, that of placing the study of human anatomy on a sound basis, on the basis of direct, patient, exact observation. And he accomplished it. Galen had attempted the same thing before him; but the times were not then ripe for such a step. Authority laid its heavy hand on inquiry, and Galen's teaching instead of being an example and an encouragement for further research, was, as we have said, made into a bible, and interpretation was substituted for investigation. Vesalius, inspired by the spirit of the new learning, did his work in such a way as to impress upon his age the value not only of the results at which he arrived, but also and even more so, of the method by which he had gained them.—SIR M. FOSTER. *Lectures on the History of Physiology.* London, Cambridge University Press, 1901.

A Study of the Cardiac Stigmata in Prolonged Human Thiamine Deficiency

By David T. Rowlands, Jr., M.D., and Carl F. Vilter, M.D.

Eight clinically proved cases of prolonged thiamine deficiency were evaluated by routine pathologic study. The microscopic features were evaluated by comparison with sections of myocardium obtained from normal individuals and individuals suffering from cardiac diseases of other varieties. No specific transitory or permanent alterations were demonstrable. It is concluded that beriberi heart disease is largely the result of a reversible biochemical abnormality and is not characterized by specific pathologic lesions.

MOST of the early studies of beriberi were carried out in the Orient[1-3] and the occurrence of the disorder is well recognized in populations in whom milled rice constitutes a large portion of the diet. In the United States it was considered little more than a medical curiosity until the studies of Weiss and Wilkins[4, 5] in the late 1930's. These authors indicated a surprisingly high incidence of beriberi heart disease (1 case in each 160 medical admissions to a large charity hospital in Boston). In many of these patients the disorder was considered to be very mild; in most instances alcoholism was a prominent feature in its pathogenesis.

During the 1940's the concept of beriberi heart disease in this country changed considerably, in some measure through the efforts of Blankenhorn,[6] who suggested relatively simple criteria for its recognition. He indicated that the disease is somewhat more common in the United States than had previously been recognized. Particular attention was directed to the common occurrence of a chronic form of cardiac failure rather than acute, high-output failure as a manifestation of beriberi heart disease. It was emphasized that other forms of cardiac disease often were complicated by the deficiency disorder. The clinical requirements for the appreciation of beriberi heart disease listed by Blankenhorn[6] were (1) enlarged heart with normal rhythm, (2) dependent edema, (3) elevated venous pressure, (4) peripheral neuritis or pellagra, (5) nonspecific alterations in the electrocardiogram, (6) no other evident cause for heart disease, (7) gross deficiency of diet for 3 months or more, and (8) improvement of symptoms and reduction of heart size after specific vitamin replacement, or (9) necropsy findings consistent with beriberi.

The cardiovascular lesions have been investigated at necropsy in human beings and in experimental animals.[4, 7] The gross pathologic features are characterized by normal or increased heart weight with dilatation and hypertrophy of one or more of the chambers. The microscopic lesions, although numerous, are nonspecific.[6] Myocardial fibers show either no alteration or varying degrees of hydropic degeneration. Striations are usually intact. Intercellular edema, congestion, hemorrhage, and swelling of connective tissue are seen. Interstitial and replacement fibrosis is also encountered.

Although it is generally agreed that complete recovery may result if beriberi heart disease is corrected at an early date, it is also maintained that recovery may be incomplete if scarring of the myocardium has resulted from the degenerative disorder.[8] The ultimate fate of the heart in treated but recurrent beriberi has not been extensively investigated.[9]

During the last 20 years a number of patients suffering from what appeared to be prolonged thiamine deficiency were examined at necropsy in the Cincinnati General Hospital. All had had heart failure at some time during their illnesses. In some, when suitably treated,

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ie cardiac failure was followed by apparent mission. In others, the recurrent episodes heart failure continued. In some, the heart ilure constituted a terminal event. It is pro-osed to record the pathologic alterations en-ountered in the hearts of patients known to ave had severe thiamine deficiency for pro-nged periods, as indicated below. This study temmed from the desire to determine whether r not there were permanent alterations super-ening upon the apparently reversible lesions f the acute form.

Materials and Methods

The diagnostic files of the Departments of Medi-ine and Pathology of the Cincinnati General Hos-pital were culled for cases coded as either "beri-beri" or "myocardosis*" on a clinical or pathologic basis. Among these there were 29 patients con-sidered to have had vitamin B deficiency in whom necropsy examination had been performed.

The criteria proposed by Blankenhorn[6] were employed as basic requirements in our clinical evaluation. In view of the desire to investigate the nature of the lesions induced by long-standing deficiency, a modified criterion of 6 months' dura-tion of deficiency (instead of 3 months) was employed. In addition, in order to be certain that the cases were truly examples of pure beri-beri heart disease, those displaying severe anemia or cardiac arrhythmia were excluded. Only 8 of the 29 cases were found to meet these limitations. These were selected for detailed clinical and patho-logic survey. Despite the small number, these were unquestionable examples of beriberi heart disease from the clinical standpoint, and therefore com-prised a suitable group for pathologic analysis. In 4 instances, there had been frank beriberi heart disease for more than 6 months and in the re-maining 4, manifestations of heart failure had existed for less than this period although thia-mine deficiency was known to have been present for 6 months or more.

Table 1 lists the salient clinical data from the 8 cases deemed suitable for this investigation. The average age at death among these patients was 50 years, with a range of 41 to 67 years. Six patients were male; all had had manifestations of heart failure and an unequivocal history of prolonged dietary deficiency. Alcoholism was a contributing factor in all but 1 patient (J.C.); psychosis was believed responsible for his poor nutrition. Three patients manifested mild eleva-tion of venous pressure. In 2 of these the venous pressure returned to normal during hospitaliza-tion; in 1 instance (G.E.) this improvement was attributed to effective thiamine therapy. In 3 cases venous pressure had not been recorded, and in 2 it was within normal limits. Evidences of peripheral neuritis or pellagra were encountered in 7 patients. There were nonspecific electro-cardiographic abnormalities in 7 instances. Five of the patients showed moderate hypertension, which, however, was not considered to militate against the diagnosis of beriberi in view of the overwhelming clinical evidence of the latter. In-deed, the hypertension tended to be variable. Cardiac failure or the transient "hypertension" common on admission blood pressure readings often accounted for the high values. On the other hand, in case G. E., there was persistent hypertension after clinical recovery from beriberi.

In 5 patients, treatment with thiamine effected an improvement of symptoms. In 1 patient (C.B.) no treatment was given. Failure of response in 2 cases is not an unusual experience.[6] One patient (J.C.) was given thiamine in a dose of 20 mg. twice a day but for only 4 days prior to death. Another patient (W.L.C.) re-ceived 100 mg. of thiamine intramuscularly every 6 hours but treatment was not begun until the day of death.

Pathologic data were gathered by a review of the descriptions of the heart recorded by the prosectors and examination of the available tissue sections. The majority of the latter had been fixed in Zenker's solution with 5 per cent acetic acid; in a few instances, 10 per cent formalin had been used. The tissues were sectioned after em-bedding in paraffin and stained with hematoxylin and eosin; 1 to 6 samples of myocardium were available in each instance (2 cases, 1 section; 1 case, 2 sections; 3 cases, 3 sections; and 2 cases, 6 sections.) Trichrome and van Gieson stains were performed in each instance to determine the extent of fibrosis. Fat stains were carried out in 3 cases in which stored, formalin-fixed, wet tissue was available. Periodic acid-Schiff stains with and without previous digestion by malt diastase were done on sections of heart from 7 of the cases of beriberi and on a group of 14 controls (4 cases of arteriosclerotic heart disease, 3 cases of hyper-tensive cardiovascular disease, 4 cases of rheumatic heart disease, and 3 normal individuals).

An attempt was made to quantitate the micro-scopic features that have, in the past, been con-sidered significant in the cardiac lesions of beriberi (vacuolization, interstitial edema, interstitial fibril-lation, replacement fibrosis).

*A category of noninflammatory disorders of the myocardium and those degenerative conditions unre-lated to coronary disease or abnormal hemodynamics.[10]

Table 1

Clinical Data

Criteria Patient	Age at death	Enlarged heart	Dependent edema	Peripheral neuritis or pellagra	Electrocardiogram	Other cause for heart disease	Duration deficiency of diet	Duration of heart disease	Improvement after vitamin therapy	Venous pressure cm. water
G.E.	53	+	1+	+	low voltage T-waves	0*	Simultaneous with onset of failure	18 yr.	+	15
W.L.C.	47	0	1+	+	low voltage sinus arrhythmia	hypertensive and arteriosclerotic, mild	10 years	1 yr.	0	—
H.R.	41	+	1+	+	low voltage T-waves. Prolonged A-V conduction	hypertension, mild	6+ years	10 mo.	+	10
J.B.	48	+	+	+	prolonged intraventricular conduction; T_3 low voltage and diphasic	0	6+ months	1 mo.	4 days' treatment without effect; death 2 days later	10
J.C.	67	+	+	+	low voltage QRS and T-waves	hypertension, mild	many years	6 wk.	No effect—treatment for 4 days	13
C.B.	44	+	+	+	premature ventricular beats	hypertension, mild	?	2 yr.	No treatment	—
H.S.	42	0	0	+		?	10 years	acute failure, death in a few hours	Initial	—
H.M.	58	0	+	0	complete A-V block	complete A-V block	2 years	2 mo.	Slight	12

*Patient G.E. developed hypertension after recovery from her initial episode of beriberi heart disease.

Table 2

Gross Pathologic Findings in Eight Cases of Beriberi

Case	Heart weight (Gm.)	Dilatation: Right atrium	Dilatation: Right ventricle	Dilatation: Left atrium	Dilatation: Left ventricle	Hypertrophy* right	Hypertrophy* left	Other diagnoses
G.E.	530	yes	yes	yes	yes	yes (7)	yes (18)	Generalized arteriosclerosis
W.L.C.	400	—	—	—	—	yes (6)	yes (16)	Status postoperative pericardial tap; anomalous left vertebral artery; generalized arteriosclerosis
H.R.	675**	yes	yes	yes	yes	— (4)	— (16)	Mural thrombi
J.B.	495	yes	yes	—	—	— (5)	— (17)	Moderate generalized and coronary atherosclerosis
J.C.	400	yes	yes	—	—	— (5)	yes (16)	Thrombosis of axillary vein; generalized arteriosclerosis
C.B.	500	—	—	—	—	— (3)	yes (16)	Coronary and aortic atherosclerosis
H.S.	310	yes	no	yes	no	— (7-10)	— (20)	None
H.M.	225	yes	no	yes	no	— (4)	— (15)	None

*Measurements are in millimeters.

**Weighed with "some excess tissue at the base."

As controls, sections of myocardium from 60 patients of comparable age were selected from the necropsy files. All of these patients were without clinical evidence of vitamin deficiency. In 20, the hearts were considered normal. Fifteen examples, each of hypertensive cardiovascular disease and inactive rheumatic heart disease, were chosen. There were 10 cases in which the underlying disease was coronary arteriosclerosis without hypertension.

The sections were repeatedly examined as unknowns and the degree of alteration was appraised in each instance. The examiner was consistently able to arrive at an identical estimate in each section.

Results

Specific pathologic examination of the hearts included those features that appeared important in excluding other forms of heart disease as well as those characteristics considered indicative of beriberi. The weights of the hearts varied from 225 to 675 Gm. (table 2). Four hearts were considered hypertrophied by weight (one of these was from the patient (G.E.), who had persistent hypertension) and 2 hearts were only slightly enlarged; the weights of 2 hearts fell within normal limits. On the basis of measurements of the thickness of the ventricles, there was marked hypertrophy of both left and right ventricles in 2 (1 with hypertension). In the other 6, the thickness of at least one ventricle was within the normal range. Observable ventricular dilatation was found in 4 cases; atrial dilatation alone was a feature of 2 others. Since the prosector's note constituted the only basis of this determination, his failure to indicate the state of the chambers did not necessarily mean that they were not dilated.

Microscopic examination revealed no significant epicardial lesions. In only 1 case was an endocardial alteration noted; this consisted of a recent mural thrombus. Vacuolization proved to be of hydropic nature (fig. 1); interstitial edema was a constant feature (fig. 2) and was often accompanied by fine interstitial fibrillation (fig. 1). Coarse fibrosis and frank collagenization were rare. Occasional infiltration with lymphocytes was observed in most cases, but they were present in only very small numbers. It was noted that there was

Table 3

Microscopic Myocardial Abnormalities in Beriberi and in Other Conditions

Cases	No. of cases	Vacuolization				Interstitial edema				Interstitial fibrils				Replacement fibrosis			
		0	1+	2+	3+	0	1+	2+	3+	0	1+	2+	3+	0	1+	2+	3+
Beriberi with more than 6 mos. of heart failure	4	0	3	1	0	0	0	4	0	0	2	2	0	2	2	0	0
Beriberi with less than 6 mos. of failure	4	1	2	1	0	0	0	4	0	0	4	0	0	4	0	0	0
Normal	20	12	6	1	1	2	12	5	1	0	19	1	0	19	1	0	0
Hypertensive cardiovascular disease	15	0	14	1	0	1	13	1	0	0	11	4	0	3	9	3	0
Coronary occlusive disease	10	4	4	2	0	2	3	5	0	0	5	5	0	0	6	4	0
Rheumatic heart disease	15	4	7	3	1	1	5	8	1	0	12	3	0	8	4	3	0

0 = none or negligible lesions.
1+ = mild alteration.
2+ = moderately severe alteration.
3+ = severe alteration.

considerable variation in the severity of muscle vacuolization, interstitial edema, and fibrosis from field to field, probably because of the mechanics of myocardial function and structure. On the other hand, the controls frequently showed changes as great as those seen in cases of beriberi (table 3).

Figures 1 and 2 represent sections of heart from cases of beriberi. Little scarring was found. Figure 3 illustrates a section of heart from a patient with hypertensive cardiovascular disease, figure 4 is from a patient with no cardiac abnormalities, and figure 5 shows the microscopic appearance of the myocardium in a patient with coronary occlusive disease. Figures 3, 4, and 5 disclose a close similarity to figures 1 and 2 in degree of interstitial edema and hydropic degeneration.

Both fat and periodic acid-Schiff stains were used in an attempt to determine the identity of the substance comprising the myocardial vacuoles. In none of the cases in which these were employed was either lipid or glycogen demonstrable. In 1 case (W.L.C.) a

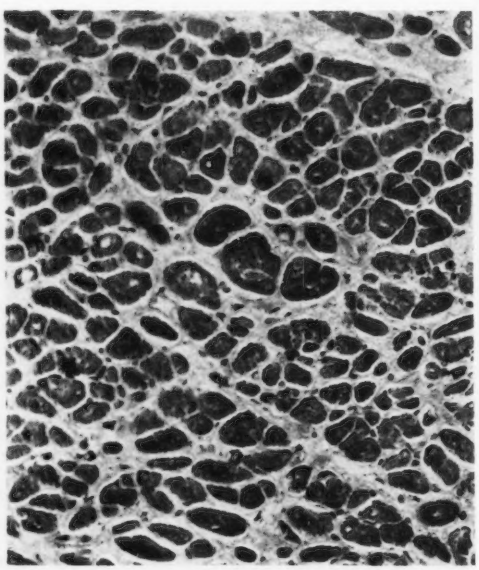

Figure 1

Microscopic section of myocardium from case C. B. Vacuolization of fibers and mild interstitial fibril formation are outstanding. (H & E stain. × 170.)

ignificant amount of perinuclear lipid was bserved. In the remaining 2 (C.B. and G.E.) mall droplets of fat were found within the uscle fibers. This group of 3 cases is beieved to be too small to permit accurate conlusions regarding the significance of accumuation of intracellular fat in beriberi heart isease. The connective-tissue stains verified he presence of fibrous tissue of the type and xtent recorded in table 3. A summary of dditional pathologic features in these paients is presented in table 4.

Discussion

The clinical criteria employed in selection of these patients were, in general, those proposed by Blankenhorn.[6] Patients suffering from disease that might simulate beriberi heart disease and those with complicating conditions that might significantly damage the myocardium were excluded. The failure of some patients to respond to thiamine is not unprecedented.[6] Moreover, the dose of thiamine in these patients was usually quite low and treatment was of short duration.

No evidence was adduced in this series to indicate a specific morphologic alteration in beriberi. On gross examination there was appreciable variation in the degree of cardiomegaly. Dilatation of cardiac chambers appeared as a more outstanding feature than an anticipated increase in weight. Indeed, the 2 hearts in this group with normal weights were described as having atrial dilatation and increase in thickness of the ventricles.

The microscopic data failed to disclose a lesion that might be called characteristic or would provoke suspicion that a lesion was of prolonged duration. It is thus apparent that one may not adequately discriminate histologically between those cases of thiamine deficiency that have had overt cardiac failure early in their course and those in whom this is only a late manifestation. Furthermore, it is not possible to discern microscopic characteristics in the myocardium of cases of beriberi significantly different from those seen in other cardiac diseases or in essentially normal hearts.

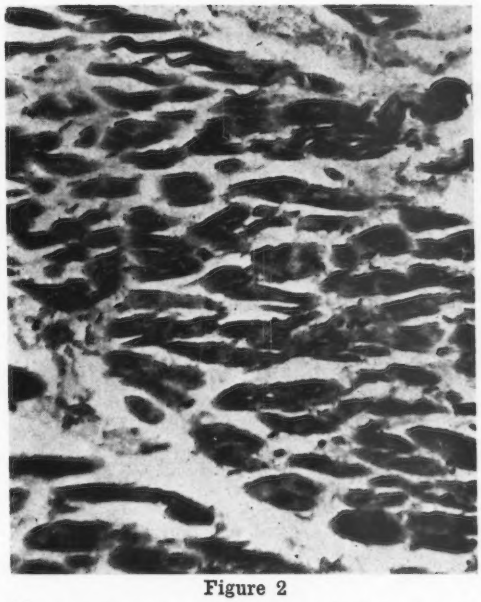

Figure 2

Microscopic section of heart muscle form case G. E. Although interstitial edema is the striking feature, hydropic alteration is also present. (H & E stain, × 170.)

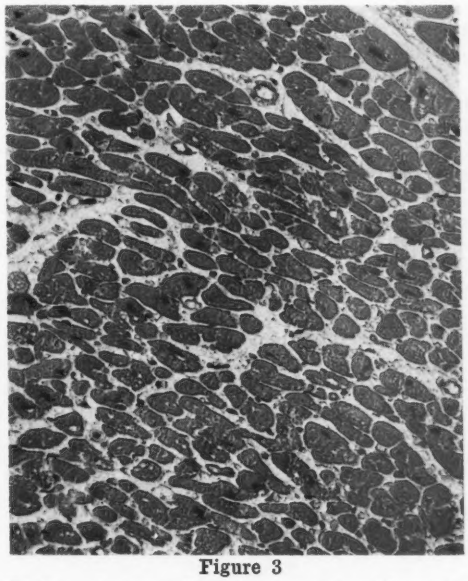

Figure 3

Section of myocardium from a case of hypertensive cardiovascular disease without beriberi, showing a similar hydropic and interstitial alteration to that seen in figures 1 and 2. (H & E stain, × 160.)

Table 4 *Summary of Additional Significant Pathologic Findings*

Case	Lungs	Liver	Alimentary tract	Genitourinary system	Nervous system	Other	Cause of death
G.E.	Atherosclerosis, moderate; infarction	Passive congestion	—	Renal infarction; leiomyomata uteri	Normal	—	Ventricular fibrillation, hypertension with cardiac failure
W.L.C.	Congestion; multiple emboli; marked fibrosis; emphysema; inactive tuberculosis	Passive congestion; central lobular necrosis	Leiomyoma-esophagus (10x5x4 mm.)	—	Cavernous hemangioma of pons. (5 mm. diam.)	Anasarca; ascites	Pulmonary edema due to beriberi
H.R.	Infarctions, 2; congestion and edema, moderate	—	—	—	Degenerative softening of cerebral cortex, left island of Reil; polyneuritis, far-advanced; degeneration in nucleus sympathicus and tracts of lateral horn, upper cervical segment of spinal cord	—	Undetermined, cardiac failure
J.B.	Hydrothorax (700 and 400 ml.); lobular pneumonia, severe	Fatty infiltration; Congestion, acute	—	Pyelonephritis, acute and chronic; benign prostatic hypertrophy	Multiple areas of encephalomalacia	—	Lobular pneumonia
J.C.	Hydrothorax (700 and 1,100 ml.); emboli, multiple; infarctions, 3; congestion; pneumonia; lobular, early	Central lobular necrosis	—	Benign prostatic hypertrophy	Not done	Axillary vein thrombosis	Pulmonary emboli, lobular pneumonia, cardiac failure due to beriberi
C.B.	Congestion; lobular pneumonia	Fatty infiltration	—	Nephrosis, toxic	Cerebral edema and congestion	Peripheral edema; generalized purpura; jaundice; ascites	Lobular pneumonia, congestive cardiac failure due to beriberi
H.S.	Lobular pneumonia; congestion and edema	—	—	—	Peripheral neuritis; slight edema and congestion	—	Pulmonary edema, lobular pneumonia
H.M.	Hydrothorax (600 and 400 ml.); congestion; early pneumonia	Posthepatitic cirrhosis; chronic hepatitis	Chronic pancreatitis, interstitial; gastric ulcer, active, penetrating; cholecystitis, chronic	Hydronephrosis, left; pyelitis, acute	Not done	—	Congestive cardiac failure due to beriberi

In the cases described, fibrosis was not a significant feature of the chronic form of the disorder. The absence of fibrosis was certainly significant in the 4 cases with prolonged cardiac failure. Follis[7] stated that severe cardiac alterations may be produced by thiamine deficiency in swine. These lesions consisted principally of necrosis that healed by scarring if thiamine was restored to the diet. Benchimol and Schlesinger[8] indicated that the myocardial damage in human beriberi was usually reversible in its initial stages. They believed, however, that in cases of long standing, the changes might be permanent and be characterized by progressive myocardial fibrosis. This fibrosis, however, could be similar to, if not identical with, that seen in other forms of heart disease. Weiss[5] stated that the myocardium could develop hypertrophy, "hydropic" degeneration, and interstitial deposition of collagen. He implied that prolonged thiamine deficiency could cause progression from an easily reversible to an irreversible condition. It is possible that scarring of the heart associated with beriberi may be the result of coexistent diseases such as coronary insufficiency. Hydropic degeneration and interstitial collagenization and edema are common in beriberi heart disease, but they are by no means specific. As noted above, they are present with equal prominence in a variety of other cardiac conditions and in normal hearts as well.

Therefore, it appears that human beriberi heart disease is largely a biochemical abnormality affecting the myocardium without inducing necrosis or other pathognomonic lesions. In each instance the patient manifested cardiac failure for which neither inflammatory, vascular, nor valvular lesions were responsible, thus justifying the designation "myocardosis." Any tissue is relatively limited in its morphologic responses to injury. Identical alterations may be encountered as a result of damage stemming from many different causes. Therefore, it is not surprising that a specific pathologic array does not present itself for beriberi heart disease.

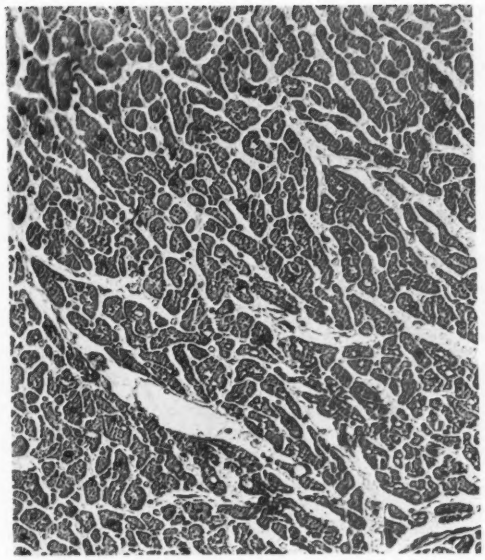

Figure 4

Section of heart from a patient with no known cardiac abnormalities. It demonstrates a striking similarity to figures 1, 2, and 3. (H & E stain, × 160.)

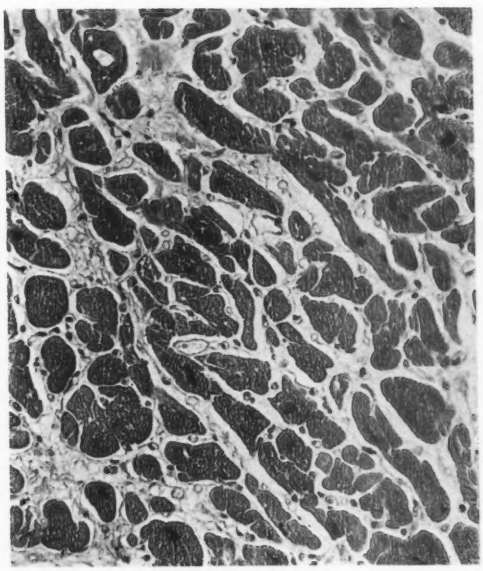

Figure 5

Microscopic appearance of heart muscle in a patient dying with coronary occlusive disease. Many of the features noted in beriberi are also present. (H & E stain, × 160.)

Since only 1 patient among those studied had adequate therapy for beriberi, followed by recurrence of the ailment, this study is inadequate to indicate the effect on the heart of treated but recurrent beriberi. However, in view of the absence of significant pathologic lesions in untreated cases of prolonged duration, it seems unlikely that such damage would occur in treated but recurrent beriberi.

Summary and Conclusions

Eight patients with clinically recognizable chronic thiamine deficiency and beriberi heart disease were investigated from a pathologic point of view in an effort to establish the presence and the extent of characteristic morphologic stigmata. In these cases there were no pathognomonic cardiac alterations at necropsy. Individuals with cardiac failure of short duration and those with prolonged heart failure manifested identical pathologic lesions.

It is concluded that beriberi heart disease is largely the result of a reversible biochemical abnormality and is not characterized by necrosis, fibrosis, or other irreversible damage to the myocardium even after prolonged periods of cardiac failure.

Summario in Interlingua

Octo patientes con chronic carentia de thiamina de clinicamente recognoscibile severitate e morbo cardiac de beriberi esseva investigate ab un puncto de vista pathologic con le objectivo de establir le presentia e le intensitate de characteristic stigmas morphologic. In iste casos nulle alterationes cardiac de character pathognomonic esseva constatate al necropsia. Individuos con decompensation cardiac de breve duration e individuos con decompensation cardiac prolongate manifestava le mesme lesiones pathologic.

Es concludite que morbo cardiac de beriberi es in grande mesura le resultato de un reversible anormalitate biochimic e es characterisate ni per necrose ni per fibrose o altere irreversibile stigmas del myocardio, mesmo post prolongate periodos de discompensation cardiac.

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Selection for Surgery of Patients with Ventricular Septal Defect and Pulmonary Hypertension

By JAMES W. DUSHANE, M.D., AND JOHN W. KIRKLIN, M.D.

Estimation of pulmonary blood flow relative to systemic blood flow is a critical point in selecting patients with ventricular septal defect and severe pulmonary hypertension for operation. A detailed medical history, physical examination, thoracic roentgenograms, careful interpretation of electrocardiograms, cardiac catheterization, and biopsy of the lung provide approaches to the problem. In borderline cases, decision still may be extremely difficult. The authors usually favor operation, however, with recognition that this decision may be in error. Obviously proper evaluation for operation cannot assure uniformly good results. Method of conduct of operation, perfusion, and postoperative care determine the results.

CONSIDERABLE difference of opinion apparently exists concerning the important matter of selecting for operation patients who have intracardiac or extracardiac shunts and pulmonary hypertension. These differences are prominent with regard to patients with ventricular septal defect and severe pulmonary hypertension. Lillehei,[1, 2] for example, has expressed the view that it is desirable to operate on nearly all patients with ventricular septal defect and pulmonary hypertension, and has implied that no patient within this group should be considered inoperable. This is in contrast to our own experience. It seemed warranted, as an introduction to a subsequent paper[3] on open-heart surgery, to present the methods that we have employed for evaluation of patients with ventricular septal defect.

Basic Premises

In patients with forms of congenital heart disease allowing shunting between the systemic and pulmonary circulations, severe pulmonary hypertension may exist in the presence of relatively normal pulmonary vascular resistance because of a pulmonary blood flow that is abnormally large in relation to the systemic blood flow. Or, pulmonary hypertension may exist in the presence of a normal or reduced pulmonary blood flow because of excessively high pulmonary vascular resistance. Variations between these two extremes occur.

It is presumed that any immediate reduction in pulmonary artery pressure after closure of a patent ductus arteriosus, atrial septal defect, or ventricular septal defect occurs as a result of reduction in pulmonary blood flow produced by the repair and possibly also as a result of reduction in pulmonary venous pressure. In some patients a reduction in pulmonary vascular resistance appears to occur in the weeks and months after operation and to contribute still further to a reduction in pulmonary artery pressure. It is believed that only when operation results in a reduction of pulmonary blood flow or pulmonary venous pressure is there an opportunity for such a later reduction in pulmonary vascular resistance.

In patients with ventricular septal defect, a reduction in pulmonary blood flow after operation can result only if pulmonary flow was greater than systemic flow prior to repair, that is, in patients in whom the shunt was predominantly left to right. If a shunt across a ventricular septal defect were bidirectional and truly equal in the two directions, repair of the defect should not result in change in pulmonary blood flow relative to systemic blood flow. On the basis of the available evidence, it is believed that under such circumstances neither an immediate nor a late reduction in pulmonary artery pressure would

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result. Although further elevation of pulmonary vascular resistance might be prevented by operation, improvement of the general status of the patient is not certain. For example, his ability to increase systemic blood flow during exercise, albeit by an increased right-to-left shunt while the defect is open, may be abolished or reduced by repair.

When pulmonary blood flow is less than systemic blood flow, the shunt being predominantly right to left, ablation of the shunt will result, *not* in a reduction of pulmonary flow relative to systemic flow, but in an increase. Since the greatly elevated pulmonary vascular resistance does not fall under these circumstances, pulmonary artery pressure must rise after repair unless total cardiac output falls. Either result is probably detrimental to the patient, and operation should be avoided. When the shunt is bidirectional and of equal magnitude in the two directions, surgical intervention is believed to be of questionable value, since reduction in pulmonary artery pressure cannot be expected to occur.

When pulmonary blood flow is greater than systemic blood flow in the presence of severe pulmonary artery hypertension, pulmonary artery pressure will be lowered by operation and the patient will be improved or returned to normal health. Operation is, in this situation, clearly indicated.

Emphasis on levels of pulmonary artery *pressure* in management of patients with ventricular septal defect can be misleading. To quote the extremes, it has been the experience at the Mayo Clinic that patients who have ventricular septal defect with essentially equal aortic and pulmonary artery pressure can be cured by operation at a low risk if pulmonary blood flow is large in relation to systemic blood flow. Equal aortic and pulmonary artery pressures also may occur in patients at present considered inoperable, that is, not amenable to improvement by operation, if pulmonary blood flow is small with a predominantly right-to-left shunt. The first group is characterized by pulmonary vascular resistance less than systemic vascular resistance, the latter by pulmonary vascular resistance greater than systemic resistance.

Methods of Estimating Pulmonary Blood Flow in Patients with Ventricular Septal Defect and Pulmonary Hypertension

It is our belief that the estimation of pulmonary blood flow relative to systemic blood flow with its implications as to pulmonary and systemic resistances becomes a critical point in the selection for operation of patients with ventricular septal defect and severe pulmonary hypertension. This problem can be approached from several aspects.

History

A detailed medical history may provide important leads concerning pulmonary blood flow. In patients with ventricular septal defect, a history of persistent cyanosis usually is obtained when systemic arterial oxygen saturation is 85 per cent or less. Cyanosis that exists when the patient is at rest is highly suggestive of a predominantly right-to-left shunt and, thus, of inoperability. Patients without a history of cyanosis usually have predominantly left-to-right shunts, although some have bidirectional shunts that are predominantly right to left but of a magnitude insufficient to produce cyanosis.

A history of repeated respiratory symptoms, often frankly associated with cardiac failure, is strongly suggestive of a continuing, large left-to-right shunt in patients with ventricular septal defect and pulmonary hypertension. At operation, such patients usually have high left atrial pressure that is restored promptly to normal by closure of the defect. High left atrial pressure and a history of continuing respiratory distress are not found in patients with ventricular septal defect and pulmonary hypertension whose shunts have become predominantly right to left. Patients with a history of pulmonary congestion and growth failure in early life, who later become asymptomatic and healthy in appearance, often exhibit this misleading apparent improvement because of marked increase in pulmonary vascular resistance and consequent reduction of the left-to-right shunt.

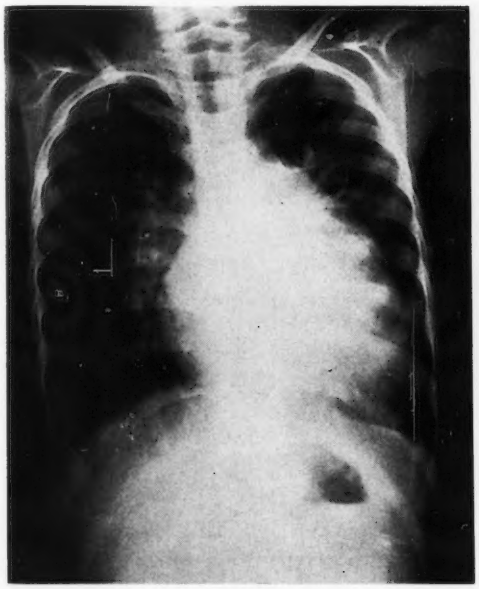

Figure 1

Roentgenogram of thorax of a 6-year-old patient with ventricular septal defect and severe pulmonary hypertension. Note that the lung fields are hyperemic and that there is general cardiac enlargement. Preoperative cardiac catheterization showed femoral artery pressure of 122/67 and pulmonary artery pressure of 109/74. A large left-to-right shunt was demonstrated. The ventricular septal defect was repaired. Fifteen months later, cardiac catheterization showed pulmonary artery pressure of 33/14 and no intracardiac shunt.

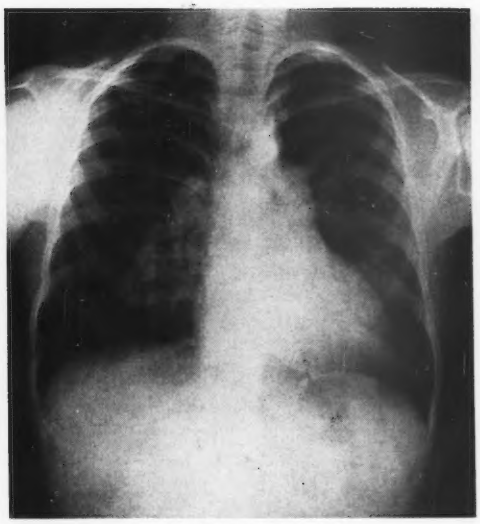

Figure 2

Roentgenogram of thorax of an 11-year-old patient with ventricular septal defect and severe pulmonary hypertension. Note that the lung fields still give evidence of being hyperemic but not so strikingly as in the case shown in figure 1. Catheterization elsewhere had disclosed pulmonary artery pressure of 96/65 while brachial artery pressure was 85/55. A left-to-right shunt of only moderate degree was demonstrated and there was considerable elevation of pulmonary resistance to 1020 dynes. sec. cm.$^{-5}$ At the time of operation, before repair, pressure in the right ventricle was 115/6 and that in the left ventricle 113/9; immediately after repair, right ventricular pressure was 62/6 and left ventricular pressure 87/8. In spite of equalization of pressures in the 2 ventricles, this patient was clearly operable because of evidence of increased pulmonary blood flow. The patient has done well.

Physical Examination

Certain features of the physical examination may give additional clues regarding intracardiac hemodynamics. A small, frail-appearing child with ventricular septal defect and pulmonary hypertension is likely to have a large pulmonary blood flow and to be greatly benefited by operation. Patients with ventricular septal defect and pulmonary hypertension whose hearts are overactive and exhibit a systolic thrill and a long, loud systolic murmur usually have a large pulmonary blood flow. Such patients often have an inflow diastolic murmur at the apex.

When physical examination reveals the heart to be quiet, without a thrill, and with only a short, soft precordial systolic murmur, the pulmonary flow is usually not large although further study may reveal it to be slightly or even moderately in excess of systemic blood flow.

Roentgenogram of Thorax

Assessment of cardiac size and contour and of pulmonary vascular shadows by means of roentgenograms of the thorax may provide valuable information concerning pulmonary blood flow and relative size of shunts. In patients with ventricular septal defect and pul-

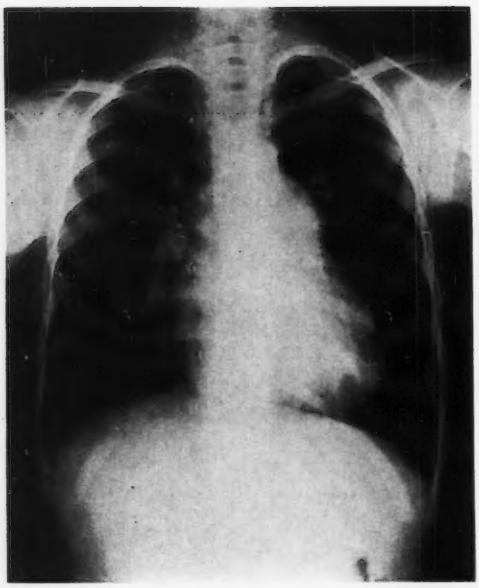

Figure 3

Roentgenogram of the thorax of a 10-year-old patient with ventricular septal defect and severe pulmonary hypertension. The roentgenogram does not give clear evidence of hyperemia of the lungs or of enlargement of the right and left ventricles. Preoperative cardiac catheterization disclosed pulmonary artery pressure of 100/67 and femoral artery pressure of 95/63; however, since pulmonary blood flow was calculated to be 6.3 liters per minute and systemic flow 4.4 liters per minute, operation was advised. Immediately after repair of the ventricular septal defect, pressure in the left ventricle was 108/5 and that in the right ventricle 76/3. The child was in satisfactory condition on dismissal from the hospital.

monary hypertension having a large pulmonary blood flow, the left ventricle is enlarged and the right ventricle is dilated as well as hypertrophied (figs. 1 and 2). In patients having bidirectional shunts of approximately equal magnitude in the two directions, the left ventricle is not significantly enlarged and the right ventricle is not enlarged or dilated although its wall is considerably hypertrophied (fig. 3). The posteroanterior roentgenogram of the thorax under these latter circumstances fails to reveal significant ventricular enlargement in contrast to the enlargement usually noted in patients with high pulmonary flow.

Enlarged pulmonary artery shadows that extend well out into the lung fields are evidence of large pulmonary blood flow. In a patient with ventricular septal defect and pulmonary hypertension, a roentgenogram that gives evidence in the lung fields of large pulmonary flow and evidence for enlargement of the ventricles would indicate that the shunt in the patient in question is predominantly left to right and that operation is indicated. Lack of evidence of hyperemia of the lungs and a cardiac silhouette that is not enlarged, save for the pulmonary artery segment, do not give clear evidence against the presence of a left-to-right shunt but do alert one to the possibility that pulmonary blood flow may not be large relative to systemic blood flow (fig. 4).

Electrocardiogram

Careful interpretation of the electrocardiogram can prove to be of considerable help in assessing the hemodynamic situation in patients with ventricular septal defect with pulmonary hypertension. Correlation of the electrocardiogram with preoperative physiologic studies and with the measured changes occurring in pulmonary artery and systemic pressures after surgical closure of the defect in a large number of children has been of considerable value in establishing and validating criteria for right and left ventricular hypertrophy or overloading.

Pulmonary hypertension resulting from any cause, whether mainly from increased pulmonary blood flow, increased pulmonary vascular resistance, or elevated pulmonary venous pressure, is reflected electrocardiographically by evidence of right ventricular hypertrophy of the systolic overloading type alone or in combination with diastolic overloading patterns. Thus, evidence of right ventricular hypertrophy is noted in virtually all cases of ventricular septal defect with severe pulmonary hypertension and is not helpful in determining whether or not the patient has increased pulmonary blood flow.

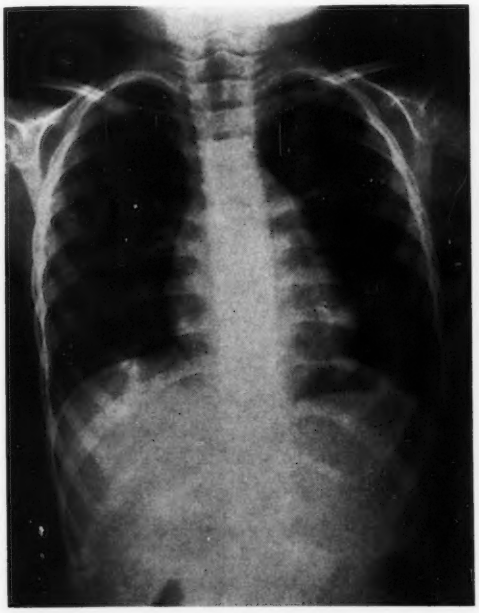

Figure 4

Roentgenogram of thorax of a 4-year-old patient with ventricular septal defect and severe pulmonary hypertension. Note the absence of hyperemia in the lung fields and normal-sized cardiac silhouette. Cardiac catheterization showed pulmonary artery pressure of 96/68 and femoral artery pressure of 96/55. The shunt across the ventricular septal defect was purely right to left and pulmonary flow was less than systemic flow. Operation was considered inadvisable.

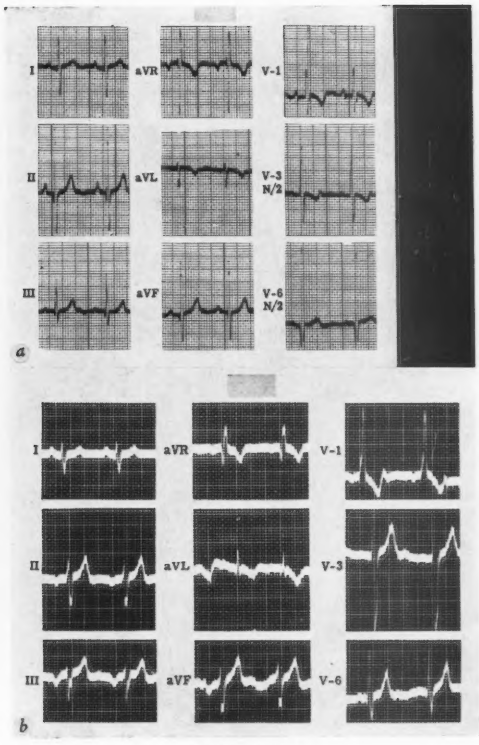

Figure 5*a*

Electrocardiogram of a 3-year-old child. Deep Q (14 mm.) and tall R (54 mm.) waves in lead V_6 constitute evidence for increased left ventricular work. A large left-to-right shunt was present and systolic pressures were 55 mm. of mercury in the pulmonary artery and 90 mm. in the femoral artery before operation with a change to 40 mm. and 110 mm., respectively, after repair of the defect.

Figure 5*b*

Electrocardiogram of an 8-year-old child. Tall, peaked T waves in lead V_6 indicate left ventricular overloading (note the small q and normal R waves). Cardiac catheterization studies indicated a left-to-right shunt of 55 per cent and the pressure in the pulmonary artery was identical with that in the aorta before operation. After repair, pulmonary artery pressure was normal.

The most important electrocardiographic contribution to the proper assessment of pulmonary blood flow in patients with ventricular septal defect and pulmonary hypertension is the information afforded concerning the left ventricle. If a dominant left-to-right shunt exists, left ventricular work is increased, but if the shunts are balanced or predominantly right to left, the left ventricle has only its normal work load. Thus, the status of the left ventricle is most important and can usually be correctly evaluated by proper interpretation of the electrocardiogram. Evidence of left ventricular increased work is detected in several ways. Leads representing left ventricular potential may have deep Q waves (more than 3.5 mm.); tall R waves (more than 25 mm.); tall, peaked T waves; prolonged intrinsicoid deflection times, or any combination of these features (fig. 5 *a* and *b*). Usually the left precordial leads (V_5 or V_6) best show these characteristics, although sometimes the leads

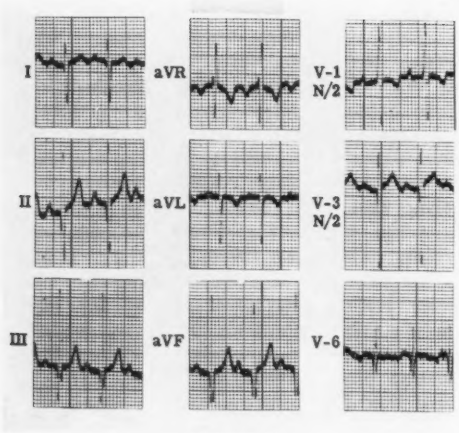

Figure 6

The electrocardiogram of a 2-year-old child. Deep Q and tall, peaked T waves in leads II, III, and aV_F indicate left ventricular overloading in this patient. Often the left ventricular potential is better represented in young children by these "vertical" leads than by the left precordial leads. A left-to-right shunt of 50 per cent was demonstrated by cardiac catheterization studies, and equal pressures in the pulmonary artery and aorta were detected. After operation, the pulmonary artery systolic pressure was 50 mm. while that in the aorta was 115 mm. of mercury.

representing vertical ventricular vectors (leads II, III, and aV_F) reflect the left ventricle more accurately in infants and young children (fig. 6). A small r and deep S wave in right precordial leads (V_1 and V_{3R}) indicate left ventricular overwork in infants and young children. Vectorial analysis of the QRS complexes of the electrocardiogram has been of considerable aid in detecting increased left ventricular work in infants and in young children less than 3 years of age. The characteristic features of these vectors are a counterclockwise QRS loop in the frontal plane with a mean QRS axis ranging from +60 to −60 degrees, normal findings in a few older children and many adolescents but usually indicative of left ventricular overloading in infants (fig. 7).

Electrocardiographic evidence of left ventricular overwork, in the absence of mitral insufficiency or aortic stenosis or insufficiency, indicates a left-to-right shunt in patients with ventricular septal defect regardless of the level of pulmonary hypertension and the degree of right ventricular hypertrophy reflected by the electrocardiogram. In some patients with nearly balanced but dominant left-to-right shunts, the electrocardiographic features of left ventricular overloading may be minimal or undetectable and thereby inconclusive, but these constitute a small percentage of cases.

Cardiac Catheterization

The most direct way of gathering data concerning pulmonary and systemic blood flow in patients with ventricular septal defect and pulmonary hypertension is by cardiac catheterization. Use of the Fick principle and of technics employing indicator-dilution curves has resulted in data of unquestioned value in patients who can be studied without heavy sedation or anesthesia. Depression of ventilation and systemic hypotension as well as possible transient changes in pulmonary vascular resistance, which sometimes occur with heavy sedation or anesthesia, may, on occasion, render difficult the interpretation of data concerning shunts in infants and small children. Catheterization performed in children without sedation or anesthesia may result in an unsteady physiologic state and may invalidate the formulas used to calculate pulmonary and systemic blood flows. Because of the reliability of the clinical criteria of increased pulmonary blood flow, it is not necessary to catheterize all patients with ventricular septal defect and pulmonary hypertension prior to operation. When these clinical criteria suggest that pulmonary blood flow is increased little, if any, but do *not* clearly indicate a reduced pulmonary blood flow, then, on clinical grounds alone, one cannot decide concerning operability. A mild to moderate increase in pulmonary blood flow may exist without being reflected in the findings at physical examination, in the thoracic roentgenogram, or in the electrocardiogram, although the instances are uncommon. Such patients should be studied by cardiac catheterization, particularly if it

can be done without sedation or anesthesia, in order to collect further data on pulmonary and systemic blood flow.

Biopsy of Lungs

It has been demonstrated that patients with ventricular septal defect and pulmonary hypertension have changes in the small blood vessels of the lungs.[4] These changes vary in type and degree and can be correlated with the ratio between calculated pulmonary resistance and systemic resistance.[5] Likewise, they can be correlated roughly with the immediate change in pulmonary artery pressure that occurs with repair of the defect,[6] although there is considerable overlap except at the extremes.

Information could be gained concerning pulmonary resistance and thus concerning pulmonary blood flow in patients with ventricular septal defect by histologic study of the pulmonary vasculature, although it might not be definitive in the individual case. Also, the reliability of other criteria of operability has rendered the need for such study unnecessary. A further reason for not resorting to biopsy of the lungs in borderline cases is the difficulty in making generalizations concerning the pulmonary vasculature from study of a small specimen from the lung.

Comment

A basic concept of operability in patients with ventricular septal defect and pulmonary hypertension has been presented. It is based not only on experience with operation in cases of ventricular septal defect but also on experience with operation in patients with pulmonary hypertension associated with patent ductus arteriosus, atrial septal defect, and other intracardiac defects. This concept would become invalid should some pharmacologic method become available for favorably affecting over a long period the severely elevated pulmonary resistance in patients who are considered at present to be inoperable.

Although the concept is clear, in occasional patients with severe pulmonary hypertension and ventricular septal defect it is difficult, in practice, to be certain of the relative magnitudes of pulmonary and systemic blood flow. In borderline cases, decision may be extremely difficult in spite of the utilization of all technics for assessing operability, including complete cardiac catheterization. In such borderline cases, we usually decide in favor of operation, with recognition of the possibility that this decision may be in error.

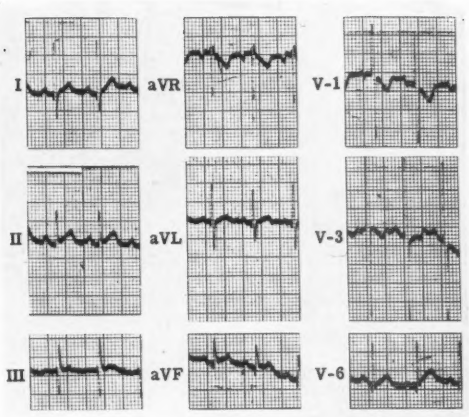

Figure 7

Electrocardiogram of a 4-month-old baby showing left axis deviation (+25 degrees) and a counterclockwise rotation of the QRS loop in the frontal plane, which are indications of left ventricular overwork. A deep S wave in lead V_1 at this age is additional evidence. The Q, R, and T waves in lead V_6 are not remarkable in this electrocardiogram. Cardiac catheterization studies indicated a left-to-right shunt of 50 per cent as well as equal pulmonary artery and aortic pressures.

An obvious final fact is that proper evaluation for operation in cases of ventricular septal defect and pulmonary hypertension cannot assure uniformly good results. The method of conduct of the operation, the perfusion, and the postoperative care determine the results.

Commentario in Interlingua

Es presentate un criterio fundamental del operabilitate de patientes con defecto ventriculo-septal e hypertension pulmonar. Illo es basate non solmente super le experientia in le operation de patientes con defecto ventriculo-septal sed etiam super le experientia in le operation de patientes con hypertension pulmonar in association con patente ducto arteriose,

defecto atrio-septal, e altere defectos intracardiac.

Le hic-presentate criterio perderea su validitate in le caso del elaboration de methodos pharmacologic pro influentiar favorabilemente e perdurativemente le severmente elevate resistentia pulmonar in patientes qui es currentemente considerate como inoperabile.

Le criterio require ab candidatos pro le intervention chirurgic inter patientes con defecto ventriculoseptal e hypertension pulmonar que lor hypertension resulta de un augmento del fluxo de sanguine pulmonar e non de un augmento del resistentia vascular pulmonar, i.e., in altere parolas, que le fluxo de sanguine pulmonar in illes excede le fluxo de sanguine in le circulation major. Le justification de iste requirimento es que le reparo del defecto ventriculoseptal reduce le fluxo de sanguine pulmonar e ergo pote effectuar un reduction del tension de sanguine pulmonar solmente si isto esseva causate per un augmento del fluxo de sanguine pulmonar e non per un augmento del resistentia vascular pulmonar.

Ben que le criterio es clar, in certe patientes con sever grados de hypertension pulmonar e defecto ventriculo-septal il es difficile in le practica esser certe del magnitudes relative del fluxo de sanguine in le circulation pulmonar e in le circulation major. In casos limine le decision es a vices difficilissime in despecto del utilisation de omne le technicas disponibile pro estimar le operabilitate, incluse complete catheterisation cardiac. In tal casos limine nos usualmente opta in favor del operation, in plen recognition del facto que iste decision pote esser erronee.

Un obvie facto final es que le correcte evaluation del operabilitate de casos de defecto ventriculoseptal in association con hypertension pulmonar non suffice pro assecurar unirformemente bon resultatos chirurgic. Le methodo secundo le qual le operation as executate, le perfusion, e le attention postoperatori es etiam factores que contribue a determinar le qualitate del resultato.

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Bell, J. F., and Meis, A.: Pericarditis in Infection Due to Coxsackie Virus Group B, Type 3. New England J. Med. **261:** 126 (July 16), 1959.

The case is reported of a 28-year-old laboratory technician who developed pericarditis after he had worked with Coxsackie virus Group B, Type 3. This virus also was recovered from the stool on 2 occasions. Repeated isolation of this virus during the acute phase of the illness and the demonstration of a rise and persistence of antibodies neutralizing the virus indicated the etiologic agent in this case.

SAGALL

Hemodynamic and Hypotensive Effects of Long-term Therapy with Chlorothiazide

By JAMES CONWAY, M.D., PH.D., AND PHILIP LAUWERS, M.D.

Long-term treatment of hypertension with chlorothiazide alone produces moderate reduction in blood pressure in 66 per cent of patients with hypertension. This fall in pressure is due to a reduction in total peripheral resistance rather than a fall in cardiac output.

THE value of any drug in the treatment of hypertension rests in the last analysis on the frequency and magnitude of its depressor effect on the blood pressure and upon whether it corrects the elevated peripheral resistance, characteristic of essential hypertension. Although the hypotensive action of chlorothiazide has been previously studied,[1-3] no attempt has yet been made to determine its usefulness in a large number of unselected hypertensive patients.

This report investigates the over-all effectiveness of long-term therapy with chlorothiazide in hypertension and studies the hemodynamic mechanism by which this treatment reduces the blood pressure.

Methods

Clinical Observations

After preliminary cardiac and renal investigation, 83 unselected ambulatory patients with hypertension were given chlorothiazide as the sole hypotensive medication. None of these patients was edematous but 16 previously had had a splanchnicectomy that had not been successful in reducing the blood pressure. The usual maintenance dose of chlorothiazide was 0.5 Gm. twice daily after an initial 3-day period of 1 Gm. twice daily. In 5 patients a larger dose of 2 Gm. per day was administered continuously. Patients were urged to reduce sodium intake by avoiding salty foods and by eliminating salt from cooking and at the table. In 14 patients blood pressure readings were taken twice daily at home and in the remainder readings were taken in the clinic. Treatment was maintained for at least 1 month in all subjects, with the exception of 7 patients who had not responded after 2 weeks and whose clinical condition required the use of more potent drugs. At varying periods after the first month of treatment the remaining patients who failed to respond were withdrawn from the investigation to be given other drugs. The average duration of therapy for the entire group was 5.4 months.

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Hemodynamic Observations

Hemodynamic studies were undertaken on 23 hypertensive out-patients in whom there was no clinical evidence of cardiac or renal failure and none had malignant hypertension. Plasma volume was measured in 10 patients and cardiac output in 16. Control observations were usually performed before starting treatment, but in 1 of the plasma-volume group and 4 of the cardiac-output group, chlorothiazide was administered first and was thereafter withdrawn or replaced by a placebo for a period of 1 month before the control observations were made. All these patients received the same dose of chlorothiazide, 1 Gm. per day, for at least 1 month before its effect was determined.

In order to study the early effects of the drug, these investigations were also performed on 7 patients before and within the 3 weeks of starting treatment. Cardiac output was measured in 4 subjects and plasma volume in 4 also.

Plasma volume was estimated by the dye-dilution method with Evans blue.[4] The total dose, which varied from 15 to 25 mg., was measured by weighing the syringe before and after each injection. After the subject had been lying down for half an hour and a control sample of blood had been drawn, the dye was injected into the antecubital vein. The needle was flushed with 5 ml. of saline before and after the injection. After 15 minutes had elapsed to allow for intravascular mixing, 4 samples of blood were drawn, without venous congestion, at 5-minute intervals from an indwelling needle in the antecubital vein of the opposite arm. Hematocrit determinations were made on the second and fourth samples of blood. The concentration of Evans blue in the plasma was measured

Table 1

Effect of Chlorothiazide on the Blood Pressure in Patients with Various Clinical Types of Hypertension

Type of hypertension	No. of cases	Blood pressure (mm. Hg) Before treatment		On chlorothiazide		Change	
		Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Essential	59	188	116	162	99	−26	−17
Post-splanchnicectomy	16	190	128	164	103	−26	−25
Malignant	4	222	126	223	121	+ 1	− 5
Renal insufficiency	4	217	129	210	122	− 7	− 7

photometrically at a wavelength of 620 mμ with a Beckman spectrophotometer. The dilution of Evans blue in plasma was estimated by extrapolation to zero time of the slope of the time-concentration curve of the 4 samples of plasma. Repeated observations in the same patient by this method gave values which were within 3 per cent of each other.

Cardiac output was measured by the dye-dilution technic with the patient in a recumbent position and without preliminary sedation. Indigo-carmine was used as the indicator[5] and injections were made through a needle lodged in the antecubital vein of the right arm, which was elevated well above heart level by 3 pillows. The dye was flushed into the vein by 5 to 10 ml. of saline and the amount of dye delivered was estimated by weighing the syringes before and after injection. The total dose varied from 34 to 42 mg. For sampling blood and recording blood pressure, a thin-walled 20-gage needle was placed in the brachial artery of the opposite arm under local anesthesia. The needle was connected by 10 cm. of polyethylene tubing to a cuvette densitometer* with filters at 620 mμ. To inscribe the dilution curve the blood was drawn through the recording instrument at a rate of 25 to 30 ml. per minute by means of a motor-driven syringe. Photographic recordings were made with gain of the instruments** arranged to give a deflection of approximately 2 cm. for 1 mg. per liter of dye. The dye-dilution curves were calibrated by drawing duplicate samples of the patient's blood containing known concentrations of dye through the densitometer immediately after the procedure. Since indigo-carmine is rapidly excreted by the kidneys, it was possible to repeat the estimations of cardiac output at each session. Three determinations were usually made in each subject in the control state and again following therapy with chlorothiazide.

*Gilford Instrument Laboratory, Elyria, Ohio.

**Research recorder and camera by Electronics for Medicine, White Plains, N. Y.

Direct blood pressure recordings were obtained before and after each dye-curve with a Statham P23A strain-gage connected to the polyethylene tubing. The mean pressure was obtained electrically by the insertion of a capacitor in the circuit. Thus it was possible to determine the cardiac output by the Stewart-Hamilton formula.[6] This, with the mean blood pressure taken almost simultaneously, was used to calculate the total peripheral resistance according to the formula:

$$TRP = \frac{Mean\ BP \times 60 \times 1332}{cardiac\ output \times 1000}\ dynes\ sec.\ cm.^{-5}$$

The serial measurements of cardiac output in the recumbent posture without premedication frequently showed variation of ± 600 ml. per minute from one estimation to the next. As a rule these changes were accompanied by simultaneous changes in heart rate and blood pressure and the first cardiac output determination was usually higher than subsequent ones. The average of observations recorded at a single session were then divided by the patient's surface area to give the cardiac index in liters per minute.

Results

Clinical Observations

To determine the frequency with which chlorothiazide affected the blood pressure in the group of 83 patients, it was arbitrarily decided that a reduction in pressure of at least 10 per cent in both systolic and diastolic levels would constitute a satisfactory response. According to this standard there were 55 responders (66 per cent) and 28 non-responders. Age, sex, or degree of cardiac involvement did not affect the frequency of response to the drug but all the patients in the malignant or accelerated phase and those with renal azotemia failed to show a fall in blood pressure (table 1). The average blood

pressure of the nonresponders was a little higher than responders; 205/122 and 185/115 mm. Hg, respectively. On the other hand patients who had undergone splanchnicectomy were unusually responsive: 12 of 16 exhibited a significant fall in pressure (table 1).

In patients with essential hypertension, the average fall in blood pressure was 26/17 mm. Hg. Consequently if the diastolic pressure is approximately 110 mm. Hg, it is probable that chlorothiazide will lower the blood pressure to normal. In our group there were 32 patients with this level of pressure and 17 were restored to normal pressure.

Hemodynamic Studies

The average control value for plasma volume in 10 patients was 2,673 ml., and after treatment with chlorothiazide, 2,582 ml. (fig. 1). When significant changes in plasma volume did occur, they were reflected in the appropriate directional changes in the hematocrit (table 2, fig. 1). The average fall in plasma volume of 90 ml. was considered to be of little physiologic consequence; nevertheless, the possibility remained that reduction in pressure could be brought about by a fall in cardiac output.

The cardiac index for the group of 16 hypertensive subjects varied between 2.6 and 5.1 L. per minute. This range was similar to that found in hypertensive patients by others[7-9] and in normal subjects studied in this laboratory under similar conditions. The average pretreatment value of 3.7 L. per minute increased to 4.1 L. per minute after treatment with chlorothiazide (table 3, fig. 2). During this time the average blood pressure measured directly from the brachial artery fell by 38.6 mm. Hg systolic and 19.6 mm. Hg diastolic. Since the cardiac output remained relatively unchanged, the fall in pressure reflected a similar decline in total peripheral resistance, from 1655 to 1259 dynes sec. cm.$^{-5}$ (table 3, fig. 2).

Three patients demonstrated a definite fall in cardiac output. In 2 of these patients the output change was more than adequate to account for the fall in blood pressure and the total peripheral resistance was increased. In 1 of these patients (Fe, table 3), the cardiac output determination was repeated after a further period of therapy with chlorothiazide. At this time, the cardiac index remained depressed, but the blood pressure had fallen further and peripheral resistance had returned to the pretreatment level.

EFFECT OF LONG-TERM THERAPY WITH CHLOROTHIAZIDE ON THE HEMATOCRIT AND PLASMA VOLUME

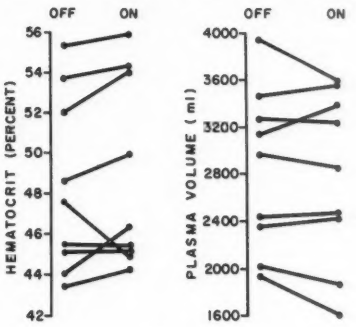

Figure 1

Effect of chlorothiazide therapy on plasma volume and hematocrit in 9 patients. OFF = control observations without treatment; ON = after at least 24 days of treatment.

Since these findings were at variance with those previously reported[2, 10, 11] in hospitalized patients given chlorothiazide for shorter periods, plasma volume and cardiac output determinations were made before and after chlorothiazide had been administered for 5 to 19 days in 7 patients (table 4). In contrast to our previous findings, these patients exhibited a considerable fall in plasma volume (average 399 ml.) and in cardiac index (average 1.0 L. per minute) (table 4).

Discussion

Effect of Chlorothiazide on the Blood Pressure

The clinical usefulness of chlorothiazide has been somewhat overshadowed by the ability of this drug to enhance the effectiveness of other hypotensive drugs.[2, 3, 12, 13] It is particularly satisfying to observe that two thirds of the patients with hypertension respond to chlorothiazide alone and that in 50 per cent of the milder cases, with diastolic pressures

Table 2

Effect of Chlorothiazide Therapy on the Plasma Volume and Hematocrit

Patient	Duration of treatment (days)	Plasma volume (ml.)	Hematocrit
Yo	0	2001	54.93
	28	*1850*	*55.91*
Zi	0	3164	47.18
	30	*3445*	*45.15*
Sc	0	4000	53.44
	42	*3602*	*53.99*
Le	0	2364	44.29
	49	*2647*	*43.74*
Ca	0	3263	45.7
	32	*3271*	*45.45*
Gu	0	1921	43.74
	60	*1603*	*46.61*
Ly	0	2967	52.23
	24	*2831*	*54.32*
Ba*	0	2500	49.38
	43	*2257*	*49.71*
Au*	0	2100	43.48
	59	*2000*	*44.07*
Bu*	0	2450	37.38
	35	*2320*	*39.29*
Mean	0	2673	47.07
	40	*2583*	*47.82*
Change	—	−90	+0.75

*These patients were also studied in the cardiac output series.

below 110 mm. Hg, it is possible to restore the pressure to normal. The proportion of patients responding to the drug and the magnitude of the hypotensive effect which we have observed is higher than that reported by others.[3, 13, 14] This discrepancy may be explained by the fact that a number of our patients had had a splanchnicectomy which, although unsuccessful in itself, made the patients more sensitive to chlorothiazide.[1]

Since the chlorothiazide compares well in effectiveness with other hypotensive drugs, it is our practice to initiate therapy with chlorothiazide alone in all patients with normal renal function. In the absence of signs indicating urgency in the reduction of pressure we find it advisable to continue such treatment for 1 or 2 months.

Table 3

Hemodynamic Effects of Chlorothiazide Therapy

Name	Duration of Treatment	Body Weight	Blood pressure		Cardiac Index	Total Peripheral Resistance
			Systolic	Diastolic		
	(days)	(lb.)	(mm. Hg)	(mm. Hg)	(L./min.)	(dynes sec. cm.$^{-5}$)
Ki*	0	175	162	98	3.5	1346
	110	*170*	*147*	*91*	*3.8*	*1180*
Bu*	0	157	211	108	3.4	1923
	35	*145*	*189*	*96*	*3.7*	*1710*
Ba*	0	180	208	92	2.6	1893
	43	*175*	*133*	*73*	*4.0*	*976*
Fo*	0	150	176	87	3.4	1559
	120	*150*	*144*	*76*	*3.5*	*1293*
Tu	0	102	238	130	4.8	2128
	60	*100*	*160*	*84*	*4.8*	*1336*
Ro	0	193	201	107	3.2	1726
	125	*178*	*156*	*85*	*2.6*	*1896*
Sk	0	202	216	124	5.1	1167
	37	*206*	*189*	*110*	*5.8*	*950*
Re	0	156	220	125	4.3	1793
	90	*140*	*147*	*112*	*4.5*	*1167*
Ev	0	151	178	103	4.2	1404
	57	*152*	*141*	*85*	*5.6*	*864*
Sa	0	143	230	140	3.8	2043
	55	*141*	*208*	*106*	*4.3*	*1616*
Lu	0	260	179	101	3.0	1749
	106	*254*	*147*	*89*	*4.4*	*865*
Hu	0	128	195	98	2.8	2128
	120	*127*	*171*	*80*	*3.7*	*1336*
Fe	0	155	208	119	4.6	1437
	50	*145*	*200*	*108*	*3.9*	*1805*
	170	*146*	*140*	*76*	*3.3*	*1423*
Au	0	165	159	90	4.3	1167
	59	*160*	*127*	*82*	*3.6*	*1085*
Sc	0	168	179	94	3.4	1521
	60	*174*	*119*	*57*	*3.9*	*910*
Du	0	134	161	91	3.5	1502
	34	*135*	*155*	*74*	*3.4*	*1439*
Mean	0	164	195	107	3.7	1655
	77	*160*	*156*	*87*	*4.1*	*1259*
Change (%)		−2.5	−19.6	−22.6	+7.5	−23.6

*In these 4 patients the observations on treatment were made first and chlorothiazide was withdrawn for a period of 4 weeks before the control observations were taken.

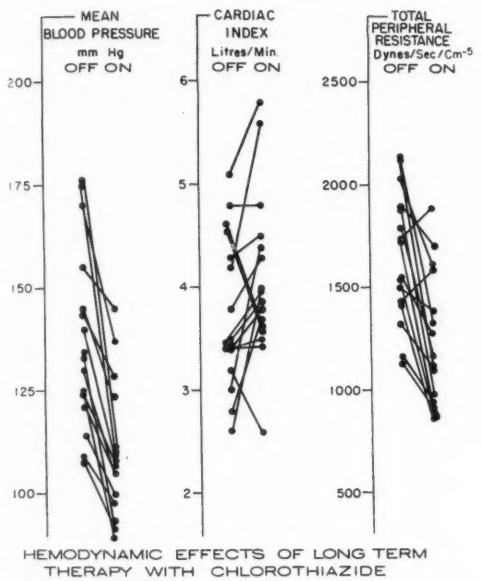

Figure 2

Effect of chlorothiazide therapy on mean blood pressure, cardiac index, and peripheral resistance in 16 patients. OFF = control observations without treatment; ON = after at least 28 days of treatment.

Table 4

Effect of Chlorothiazide Administered for Short Periods (five to nineteen days) on Blood Pressure, Plasma Volume, Cardiac Output, and Peripheral Resistance

Name	Duration of Treatment (days)	Mean Blood Pressure (mm. Hg)	Plasma Volume (ml.)	Cardiac Index (L./min.)	Total Peripheral Resistance
Co	0	144*	2296	—	—
	8	*135*	*1986*	—	—
Ho	0	143*	4156	—	—
	6	*146*	*3420*	—	—
Ha	0	170*	2486	—	—
	15	*147*	*2169*	—	—
Jo	0	149	6014	2.9	2038
	5	*148*	*5780*	*2.5*	*2344*
Au	0	115		4.3	1167
	12	*105*	—	*3.1*	*1407*
Ro	0	139	—	3.2	1726
	19	*134*		*2.2*	*2381*
Re	0	175	—	4.3	1793
	10	*112*	—	*3.2*	*1573*
		148	3738	3.7	1681
Mean	*11*	*132*	*3339*	*2.7*	*1926*
Change %		−10.5	−10.7	−21.7	+14.6

*In these patients the blood pressure was measured indirectly and mean pressure estimated as diastolic pressure plus 1/3 of the pulse pressure.

Mode of Action

During the initiation of chlorothiazide therapy, there is a fall in body weight and an associated loss of extracellular fluid volume[2] and of plasma volume.[2, 10] As a result cardiac output falls.[10, 11, 15] Our data confirm this and differ from those of Aleksandrow et al.,[16] who found no change in cardiac output after 5 days of chlorothiazide therapy. Since restoration of plasma volume by the infusion of dextran will restore the blood pressure to its previous level,[10, 15] it seems undeniable that the initial fall in blood pressure is the simple hemodynamic consequences of oligemia. From the functional point of view this state is not entirely satisfactory, since calculated peripheral resistance rises and blood pressure reduction is achieved at the expense of blood flow to the tissues.

In contrast, long-term therapy with chlorothiazide appears to maintain the reduction in blood pressure by different means; plasma volume is restored toward normal and cardiac output returns to its previous level while the blood pressure reduction continues. This change is physiologically more satisfactory, since it shows that this drug eventually produces a functional reversal of the increased arterial resistance characteristic of hypertension.

The reason for this change in the mode of action of the drug is not evident. It may be due to a separate action of the drug that develops more slowly or to a readjustment of the peripheral resistance in response to the earlier oligemic phase. Another possibility, suggested to us by Dr. Freis, is that the later stage may result from the gradual improvement in the underlying hypertensive disease process brought about by the reduction of blood pressure, a mechanism similar to that suggested by Perry and Schroeder after long-term therapy with hexamethonium and hydral-

azine.[17] It is difficult to choose between these alternatives; but we would favor the concept of a distinct action of chlorothiazide, either direct or indirect, on the blood vessels. The reasons for this are that the period of approximately 1 month is too short a time to effect a reversal of the hypertensive process. Although ganglion blockers reduce cardiac output, long-term therapy does not lead to a fall in peripheral resistance.[18] Furthermore, the continuing antihypertensive effect of chlorothiazide may be demonstrated by the elevation in pressure that occurs when the drug is withdrawn. Finally the gradual restoration of plasma volume and exchangeable sodium[19, 20] shows clearly that the equilibrium, which is finally reached between the diuretic effect of the drug and the homeostatic mechanisms, differs considerably from the initial oligemic state.

The nature and distribution of the change in peripheral resistance have yet to be determined before the true value of chlorothiazide therapy can be assessed. Whatever the final mechanism of action turns out to be, this study points out once again the need for studying the peripheral vascular bed in searching for the cause or cure of hypertension.

Summary

The value of long-term therapy with chlorothiazide as the sole antihypertensive drug has been investigated in 83 patients with hypertension. A significant fall in blood pressure was found to occur in 66 per cent of patients; the average reduction in pressure in patients with essential hypertension was 26/17 mm. Hg.

After 1 or 2 weeks of therapy the plasma volume and cardiac output fell and total peripheral resistance increased.

After 1 month or more of continued treatment plasma volume and cardiac output were restored to pretreatment levels while the fall in blood pressure was maintained. Long-term therapy has therefore produced an action on the peripheral vessels leading to a reduction in total vascular resistance.

Summario in Interlingua

Le valor del uso de chlorothiazido como sol agente antihypertensive in therapia a longe vista esseva investigate in 83 patientes con hypertension. Esseva trovate que un grado significative de reduction del tension de sanguine occurreva in 66 pro cento del casos. Le reduction medie del tension in patientes con hypertension essential amontava a 26/17 mm de Hg.

Post 1 o 2 septimanas de therapia, le volumine del plasma e le rendimento cardiac descendeva e le total resistentia peripheric montava.

Post 1 mense o plus de tractamento continue, le volumine del plasma e le rendimento cardiac esseva restaurate al nivellos pretractamental durante que le reduction del tension de sanguine esseva mantenite. Le conclusion es que le therapia a longe vista con chlorothiazido exerceva un effecto super le vasos peripheric que resultava in un reduction del total resistentia vascular.

Acknowledgment

We would like to acknowledge the generous and enthusiastic help of Dr. S. W. Hoobler throughout this study, and to thank Dr. J. Beem, of Merck, Sharp and Dohme, for the supplies of chlorothiazide used in this study.

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Medical Eponyms

By Robert W. Buck, M.D.

Pardee's Sign. Harold E. B. Pardee (b. 1886) Assistant Professor of Clinical Medicine at the Cornell University Medical College described "An Electrocardiographic Sign of Coronary Artery Obstruction" in the *Archives of Internal Medicine* 26:244-257 (August) 1920.

"It is hoped to show that obstruction of a branch of the coronary artery is followed by a sign which is characteristic of this condition and is readily recognizable in the human electrocardiogram. . . . The characteristic changes appearing a day or two after the obstruction are as follows: The QRS group is usually notched in at least two leads, and usually shows left ventricular preponderance. The T wave does not start from the zero level of the record in either Lead I or Lead III though, perhaps, from a level not far removed from it, and in this lead quickly turns away from its starting point in a sharp curve, without the short straight stretch which is so evident in normal records preceding the peak of the T wave. The T wave is usually downward in Lead II and in one other lead. Not all of these changes are to be found in every record, but enough of them are present to give it a characteristic appearance."

Secondary R Waves in Right Precordial Leads in Normal Persons and in Patients with Cardiac Disease

By FERNANDO A. TAPIA, M.D., AND WILLIAM L. PROUDFIT, M.D.

Secondary R waves in leads V_1 or V_{3R} are definitely abnormal if the primary R wave is high for the age group even though the R′ is small; if the secondary R wave is more than 6 mm.; or if the R′/S ratio exceeds 1. Other patterns may be found both in patients with heart disease and in normal subjects. In the abnormal cases, the QRS changes persist in leads taken below but in line with V_1 and V_{3R}; but in normal cases, the secondary R waves usually disappear in the lower leads.

CONSIDERABLE disagreement exists concerning the clinical significance of secondary R waves in right precordial leads in instances in which the duration of the QRS complex is normal or slightly prolonged. Their presence is frequently interpreted as indicative of incomplete right bundle-branch block and often is considered a manifestation of cardiac abnormality. Several investigators[1-5] have reported the high incidence of secondary R waves in 1 or more of these leads, including additional higher or more lateral chest leads in normal persons.

No uniform criteria are available to differentiate the electrocardiograms of patients who appear to have cardiac disease from those of normal persons having secondary R waves in right precordial leads. In an attempt to find reliable differential criteria, the electrocardiograms of patients with proved cardiac disease and those of normal persons showing secondary R waves in any lead from the right side of the precordium were compared. Additional lower and higher chest leads were taken to observe any differential variation in both groups.

A distinct pattern was found in the majority of patients with cardiac disease, especially in those with congenital cardiac disease. The findings in right lower chest leads seemed to be of sufficient clinical value to clarify the significance of controversial patterns.

From the Department of Cardiovascular Disease, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

Material and Methods

The routine 12-lead electrocardiogram and additional right chest leads were studied in 63 persons having secondary R waves in 1 or all of the right precordial leads, with "incomplete right bundle-branch block" pattern. Twenty-five of the patients had congenital heart disease producing right ventricular overload; 13 had acquired heart disease; and 25 were normal from the cardiovascular standpoint.

The diagnosis in the 25 patients with congenital heart disease was confirmed by cardiac catheterization and selective cineangiocardiographic studies.* The patients (12 female and 13 male) ranged in age from 6 months to 36 years. Ten had interatrial septal defect, 4 had interventricular septal defect, 4 had pulmonic stenosis, 2 had anomalous pulmonary venous return, 2 had a combination of interatrial septal defect and anomalous pulmonary venous return, and 1 each had tetralogy of Fallot, aortic-pulmonary window, and Eisenmenger's complex. The diagnosis was confirmed by cardiac surgery in 20 of these 25 patients.

The 13 patients (5 female and 8 male) having acquired heart disease ranged in age from 19 months to 61 years. The disease was caused by rheumatic valvular disease (3 patients), arteriosclerotic heart disease (4 patients), pulmonary heart disease (2 patients), lupus erythematosus and collagen diseases (2 patients), myocarditis (1 patient), and carcinoid syndrome (1 patient). Fewer patients were selected for this intermediate control group than for each of the other groups because of difficulty in determining the significance of the organic lesion.

The 25 persons with normal hearts ranged in age from 2½ to 60 years and included 9 females and 16 males. In each there was no evidence of heart disease by history, physical examination, or radiologic cardiac evaluation, and there were no

*Studies carried out by F. Mason Sones, Jr., M.D.

other electrocardiographic abnormalities. The secondary R waves in the right precordial leads were detected during routine electrocardiographic evaluation for periodic examination, preoperative clearance, or diagnostic studies. This group included 3 patients with initial questionable evidence of congenital heart disease, because of the presence of an R′ in right precordial leads and a pulmonic systolic murmur, but without symptoms or cardiac enlargement by radiologic or fluoroscopic examination. In all 3 (1 had pectus excavatum) cardiac catheterization and selective cineangiocardiographic studies revealed normal intracardiac hemodynamics.

In all 63 patients, routine 12-lead electrocardiograms were taken. Nine chest leads were recorded with a paper speed of 75 mm. per second and a normal standardization: V_{3R}, V_1, and V_2 at the usual levels and leads V_{3R}, V_1, and V_2 at lower levels, 1 and 2 interspaces below the usual levels. In 8 patients, additional higher right chest leads were recorded. All records were made with a Sanborn Twin-Beam Cardiette Model 62. In each of the leads the following observations were recorded: incomplete right bundle-branch block pattern, QRS duration, time of inscription of R and R′, amplitude of R and R′, depth of S waves, direction of T waves, presence of slurring or notching, or both, of the QRS complexes, and the R′/S ratio in V_1 and V_{3R}. Concomitant presence or absence of a relatively broad S in lead I, V_5, V_6, and of a secondary R wave in lead aV_R of the routine electrocardiogram were also noted and the R′/S or R/Q ratio in aV_R was recorded. Patients with complete right bundle-branch block (QRS more than 0.12 second) were not included in this study.

Findings

From the study of the routine electrocardiogram in the 3 different groups, several findings appeared to be helpful in differentiating "pathologic" from "physiologic" secondary R waves in the right precordial leads. However, no specific criterion was consistently found. Definite identification of abnormality was possible in 20 (80 per cent) of the 25 patients with congenital heart disease and in 6 (46 per cent) of the 13 patients with acquired heart disease.

The criterion for diagnosis of incomplete right bundle-branch block (the presence of a late secondary R in right precordial leads with a QRS duration less than 0.12 second)[6, 7] was present in all the normal subjects. Stricter criteria for such a diagnosis (QRS interval 0.08 or 0.10 to less than 0.12 second[8–11]) were satisfied in a large percentage of the normal subjects and in a frequency equal to that of patients with definite involvement of the right heart. Secondary R waves considered to be without diagnostic significance for right ventricular hypertrophy[9, 10, 12–14] were found in many patients with heart disease and definite right ventricular hypertrophy.

The time of the inscription of the initial R in the right precordial leads was less than 0.03 second in all patients, and the R′ (0.03 to 0.035 second being considered as maximum normal values[15–18]) was delayed in all patients. Slurring or notching of the QRS complex and the presence of a relatively broad S in leads I, V_5, and V_6 were found to be similar in incidence in the normal and abnormal groups. Most of the patients in both groups had inverted T waves in leads V_1 and V_{3R}.

Presence of R′ in aV_R and R′/S or R/Q Ratio in aV_R

A secondary R wave in a V_R, considered to be "a highly reliable indication of so-called incomplete right bundle-branch block"[5] was present in only 12 of 25 patients with congenital heart disease, in 9 of the 13 patients with acquired heart disease, and in 14 of the 25 normal subjects showing secondary R waves in right chest leads.

An "abnormal" R/Q or R′/S ratio in aV_R (more than 1.0)[12, 19] was present in only 3 patients of the congenital group, in only 2 patients with acquired heart disease, and in 1 normal subject.

Amplitude of R and R′ and Comparative Values

Most of the patients in the 3 groups had small initial R waves exceeded by the secondary R waves (fig. 1). The highest primary R in normal subjects was 8 mm. in V_1 in a 2½-year-old child. Primary R waves larger than 8 mm. in V_{3R} or V_1 were present only in patients with heart disease. The highest R′ recorded was 25 mm. in a patient having congenital heart disease. The amplitude of R′ in the patients having no heart disease did not exceed 6 mm. except in 1 case in which the abnormal pattern persisted in right lower

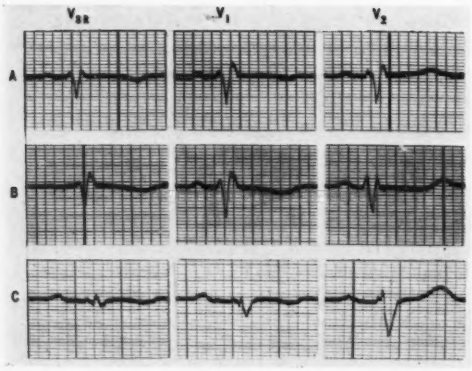

Figure 1

A *(normal) and* B *(congenital heart disease) showing similar patterns.* C. *Small R′ in congenital heart disease. R′/S ratio greater than 1.0.*

chest leads. Small secondary R waves (less than 6 mm.) were found in a significant number of patients with heart disease (fig. 1*B* and *C*) (12 of 25 with congenital heart disease and 10 of 13 with acquired heart disease).

Additional data obtained by reviewing 30 more electrocardiographic records with "incomplete right bundle-branch block" pattern in patients with interatrial septal defect revealed findings similar to those presented for the congenital group.

Depth of S and the R′/S Ratio in V_1 and V_{3R}

A relatively small S with R′/S ratio more than 1.0 in V_1 or V_{3R} was found in most (19 of 25) of the patients with congenital heart disease, less frequently (6 of 13) in patients with acquired heart disease, and in only a few (4 of 25) of the patients with clinically normal hearts. In the latter group, of the 4 patients with R′/S ratio more than 1.0 in V_1 or V_{3R}, 3 had persistent R′ and 1 showed a notched tall R on the right lower chest leads.

The R′ in Right Lower Chest Leads

When additional right lower chest leads were taken (table 1), rather striking and consistent differences in the secondary R waves were found between the patients with definite heart disease and those with clinically normal hearts.

In all patients with congenital heart disease, the secondary R wave persisted or

Table 1

R′ in Right Lower Chest Leads in Sixty-three Patients

R′ in lower chest leads	Number of Patients Having: Congenital heart disease	No heart disease	Acquired heart disease
Persistent	22 (88%)	4* (16%)	10 (77%)
Change to notched R	3 (12%)	1* (4%)	1 (8%)
Disappear in all leads		20 (80%)	2† (15%)

*R′/S ratio in $V_1 > 1.0$ except in one of normal cases with persistent R′.
†No right ventricular hypertrophy.

changed to an abnormal QRS shape. In the majority, R′ persisted unchanged; and in a few, the RSR′ complex changed to a tall notched R with incomplete fusion of R and R′. In all patients of this group, the S wave of the "M"-shaped complex decreased progressively in depth with maintenance of a true R′ in the right lower chest leads (fig. 2). In 3 patients, however, the S wave became a central notching of the R wave above the baseline with disappearance of the true R′ but with persistent "M"-shaped contour. One of these patients had an interatrial septal defect without pulmonary hypertension and the other 2 had pulmonic stenosis with a QRS pattern in lower leads resembling more closely that of the "systolic overload" frequently seen with the latter defect.

Similarly, most of the patients with acquired heart disease showed persistent R′ in right lower chest leads. In 1 patient with systemic lupus erythematosus the R′ changed to a notched R. In 2 patients with asymptomatic rheumatic heart disease and mild mitral insufficiency, the R′ disappeared in the lower leads; neither of these patients had clinical or radiologic evidence of cardiac enlargement or right ventricular hypertrophy.

In contrast, the R′ disappeared in most of the subjects with clinically normal hearts when additional leads were taken 1 and 2 intercostal spaces below the routine levels. The

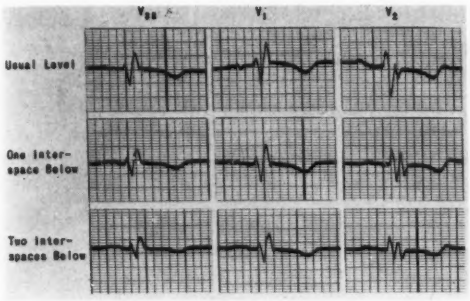

Figure 2

Persistent R′ in lower leads (interatrial septal defect). R′ is 8 mm. and the R′/S ratio greater than 1.0 in V_1.

R′ disappeared by gradual reduction in its amplitude and without significant changes of the S wave (figs. 3 and 4). In about half of this group, the R′ disappeared in all 3 leads when additional leads were taken 1 interspace below usual levels; and in the other half, the R′ disappeared when additional lower chest leads were taken 2 interspaces below routine levels. However, 4 patients showed persistent R′ in lower leads, even 2 interspaces below usual levels, 3 of them having small S waves and abnormal R′/S ratios in the routine V_1 or V_{3R} lead. Two of these 4 patients, aged 45 and 49 years, respectively, were seen for routine annual physical examination and were apparently in good health. The third patient, 49 years of age, had obesity and functional hypoglycemia, and the fourth aged 50 years was suffering from hyperthyroidism but without clinical evidence of cardiac involvement. A 27-year-old man with a diagnosis of left lower lobe bronchiectasis showed a tall notched R in right lower chest leads and he also had an R′/S ratio over 1.0 in the usual V_1 and V_{3R} leads. In all the 3 patients with initial questionable evidence of congenital heart disease in whom the diagnosis was disproved by subsequent studies, the secondary R wave disappeared in lower leads.

Correlation between RSR Patterns, Heart Disease, and Persistent R′ in Lower Chest Leads

The most common pattern found in normal persons was a small R, a relatively deep S wave with R′/S ratio less than 1.0, and a small

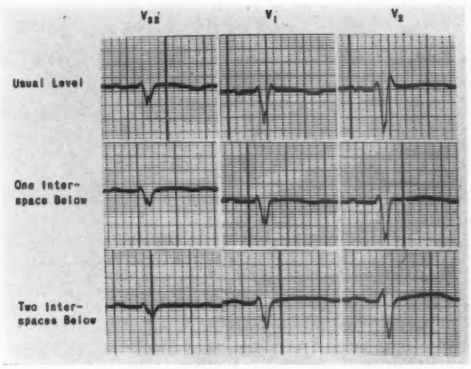

Figure 3

Disappearance of R′ in lower lead and R′ absent in V_{3R} (normal).

R′ (6 mm. or less)—rSr′ pattern—and in all, with one exception, the R′ disappeared in lower chest leads (tables 2 and 3). Patients with heart disease having a similar pattern showed persistent R′ in right lower chest leads.

The majority of patients with heart disease, especially those of the congenital group, had a small S wave with an R′/S ratio greater than 1.0, or an R′ larger than 6 mm., or a primary R larger than 8 mm. In all these cases the abnormal pattern persisted in lower leads as it was observed in the few patients with normal hearts having similar patterns.

R′ in Upper Leads

In all patients in whom additional right upper chest leads were taken, the R′ showed an increase in amplitude, regardless of the presence or absence of heart disease. In many normal subjects, secondary R waves appeared in higher leads, not present in the correlative lead at routine level.

Comparative Amplitude of R′ in V_{3R} and V_2

When a secondary R wave was present in all 3 usual V_{3R}, V_1, and V_2 leads, it tended to be higher in V_{3R} in the patients with heart disease (11 of 14 patients) than in those without heart disease and higher in V_2 in those without (7 out of 10) than in those with heart disease. The secondary R wave was present in V_{3R} in all but 1 of the patients with heart disease; the exception was a patient with mild

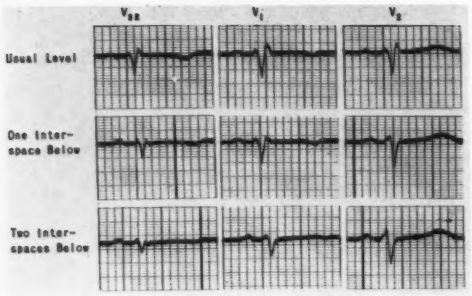

Figure 4
Disappearance of R′ (normal).

mitral insufficiency having no evidence of right ventricular enlargement and in whom the R′ disappeared in the right lower chest leads. In 3 normal subjects, the R′ was absent in V_{3R} but present in V_1 and V_2; and in all, the R′ disappeared when right lower chest leads were taken (fig. 3).

The R′ was present in V_{3R} alone in 3 patients with congenital heart disease, in 2 with acquired heart disease, and in 1 normal subject. In all these cases, it persisted when right lower chest leads were taken.

Discussion

The presence of a secondary R wave in right precordial leads per se does not mean electrocardiographic or clinical abnormality. It may be present in patients with definite heart disease and in those with clinically normal hearts. In this study, certain associated electrocardiographic changes were found in most of the patients of the abnormal group (especially in those with congenital heart disease) but in few of the patients in the normal group. When routine chest leads were used, a definite diagnosis of abnormal secondary R wave in right precordial leads was established in 20 (80 per cent) of the 25 patients with congenital heart disease and in 6 (46 per cent) of the 13 patients with acquired heart disease. However, a significant number of the patients with heart disease showed secondary R waves in routine right chest leads that could not be differentiated from those found in the normal subjects, and accepted diagnostic criteria of "incomplete right bundle-branch block" were present in the majority of subjects with clinically normal hearts.

From the analysis of our findings, the most reliable diagnostic signs of abnormal or pathologic RSR pattern in right precordial leads were (1) a primary R higher than 8 mm. in V_{3R} and V_1, regardless of the amplitude of the secondary R; (2) a secondary R wave higher than 6 mm., regardless of the amplitude of the primary R; and (3) a small S with an R′/S ratio more than 1.0 in V_1 or V_{3R} or both (tables 2 and 3). When R′ was higher than R, it was not significant for abnormality unless the R′ exceeded 6 mm. in height or the R′/S ratio exceeded 1.0. It seems that a large R′ in right precordial leads (apparently greater than 6 mm.) whether it is larger or smaller than the primary R, is definitely abnormal. On the other hand, an R′ less than 6 mm., whether it is larger or smaller than R, is not necessarily abnormal. However, when large primary R waves exceed normal-range values for the involved age group,[15, 16, 18, 20] and are consistent with right ventricular hypertrophy,[8, 21–25] the presence of an R′ (even if less than 6 mm.), is confirmatory of right ventricular hypertrophy or abnormal electrocardiogram. Small secondary R waves (less than 6 mm.) but larger than S (R′/S ratio more than 1.0), were also considered abnormal (fig. 1*C*).

In the 3 groups, all cases with an R′/S ratio in V_1 or V_{3R} of more than 1.0 had a persistent R′ in lower leads (table 3). The fact that an R′/S ratio less than 1.0 in these leads was present in the electrocardiograms of all normal subjects in which the R′ disappeared in lower chest leads (with one exception) and the observation that a ratio more than 1.0 was present in 19 (76 per cent) of the 25 patients with congenital heart disease, make its presence a reliable criterion of abnormality but its absence does not exclude organic changes.

The presence of a secondary R wave in right chest leads in the absence of the 3 previously mentioned criteria may still represent an

Table 2

RSR Patterns in Sixty-three Patients

	Number of Patients Having		
	Congenital heart disease	No heart disease	Acquired heart disease
rSr′ (Relatively deep S with R′/S < 1.0 + R′ < 6 mm.)	5 (20%)	21 (84%)	7 (54%)
rsR – RsR – Rsr (Small s + R′/S > 1.0 + R′ > 6 mm. or R > 8 mm.)	15 (60%)	1* (4%)	3 (23%)
rsr (Small s + R′/S > 1.0 + R′ < 6 mm.)	5 (20%)	3* (12%)	3 (23%)

*Persistent abnormal pattern in lower leads.

electrocardiographic abnormality and differentiation from those patterns seen in persons with normal hearts is more difficult. It was evident that a relatively deep S wave (R′/S ratio less than 1.0) and a small R′ (6 mm. or less) were present in practically all the normal subjects in whom R′ disappeared in lower chest leads (fig. 1*A*), but some patients with congenital and acquired heart disease had similar patterns (fig. 1*B*). Therefore, the differentiation of physiologic and abnormal secondary R waves cannot be established on the basis of this pattern alone (table 2). However, there were several associated findings suggesting that the R′ represented a normal electrocardiographic variation and not a manifestation of heart disease. The above pattern in V_1 or V_2, or both, but not in V_{3R} was seen only in subjects with normal hearts (fig. 3) and in one patient with rheumatic heart disease without right ventricular enlargement in whom the R′ disappeared in lower leads. The same pattern with R′ in V_2 larger by more than 1 mm. than the R′ in V_{3R}, was also present in several normal subjects but in none of the patients with heart disease.

The presence of a secondary R wave with an R′/S ratio more than 1.0 in V_{3R} alone seems abnormal. In all cases in which R′ was present in V_{3R} alone, it persisted in lower leads, suggesting definite abnormality.

In doubtful cases, the use of additional right lower chest leads may be helpful in differential diagnosis; it permitted the establishment of a differential criterion in those cases of indeterminate pattern, common to patients with and without heart disease. There was a consistent correlation between abnormal RSR patterns, heart disease, and persistent secondary R waves in right lower chest leads (table 3). The R′ persisted in lower leads in all patients with RSR patterns interpreted as abnormal (figs. 1*C* and 2) and in all patients with heart disease showing indeterminate or not definitely abnormal RSR patterns. The possibility of an organic conduction defect without clinically detectable heart disease cannot be excluded in those few patients whose R′/S ratios were abnormal in V_1 and V_{3R} and in whom the R′ persisted in lower leads. The secondary R wave disappeared in all but one of the normal subjects showing indeterminate RSR pattern in conventional right precordial leads (figs. 2 and 3).

A persistent R′ in right lower chest leads probably indicates an organic change, either a disturbance in the conduction system or right ventricular hypertrophy. Whatever the position of the exploratory electrode, the abnormal conduction pathway or delayed activation of hypertrophied muscle of the basal zones should be recorded. On the other hand, secondary R waves in right precordial leads that disappear when right lower chest leads are taken, as found in all young healthy subjects in our study and in most of the adult group with clinically normal hearts, may be due to a variable distribution of the areas on

Table 3

Criteria of Abnormal RSR Pattern, Heart Disease, and Persistent R′ in Lower Chest Leads in Sixty-three Patients

Pattern	Description	Clinical Heart Disease	Persistence of R′	Disappearance of R′
rsr	Small s +	Present	26	0
rsR Rsr RsR	R′/S > 1.0 or R′ > 6 mm. or R > 8 mm.	Absent	4	0
rSr	Large S +	Present	11	1*
	R′/S < 1.0 or R′ < 6 mm.	Absent	1	20

*Patient with mild mitral insufficiency without right ventricular enlargement.

the surface of the chest to which the normal potential variations of the ventricular surfaces are transmitted. Sequence of mural and septal activation are detected, therefore, in different ways according to the changes in the position of the electrode and to variations in the position of the heart rather than to changes in intraventricular conduction due to organic defect.

The fact that secondary R waves were progressively larger or first appeared when higher chest leads were taken in our patients —a frequent finding by Overy and Johnston[1] and by Said and Bryant[3, 4] in young healthy adults—corroborates the above impression. This observation supports the view that secondary R waves in normal subjects may be due to physiologic late activation of muscle near the outflow tract of the right ventricle,[2, 26] more specifically of the crista supraventricularis[27] or of the basal zones represented by the direction of the terminal portion of the QRS vector,[28] and may be best detected with high right chest leads and are not recorded when the electrode is displaced to right lower chest positions.

The use of additional right lower chest leads—specifically V_{3R} or V_1 recorded 2 interspaces below usual levels—in doubtful cases of so-called incomplete right bundle-branch block, seems more reliable than the use of lateral right chest leads to differentiate the pathologic from the physiologic presence of secondary R waves in the usual right precordial leads. Overy and Johnston[1] have suggested that in subjects without heart disease, secondary R waves may occur in high right chest leads but are absent in lateral right chest leads; however, Said and Bryant[4] found secondary R waves in right lateral chest leads at the level of the fourth and fifth intercostal spaces in 73 per cent of 100 young healthy adults.

Our findings do not entirely agree with those of Camerini and Davies,[2] who found a higher incidence of R′ in leads obtained from one intercostal space below V_{5R}, V_{4R}, and V_{3R} than we found; but they reported a total incidence of R′ in any additional lead and no correlative changes 1 and 2 interspaces below usual levels.

An apparently contradictory disappearance of secondary R waves in right lower leads was seen in 2 patients with rheumatic heart disease. Each had asymptomatic mild mitral insufficiency without clinical or radiologic evidence of right ventricular enlargement, and an R′/S ratio in lead V_1 of less than 1.0; one showed an R′ only in V_1 and V_2 and none in V_{3R}. The R′ was probably a physiologic variation and not the result of right bundle-branch block or right ventricular hypertrophy, this interpretation being more in accordance with the entire clinical picture. These findings suggest the possible value of additional lower chest leads in interpreting the presence of intermediate secondary R waves in right precordial leads in patients with rheumatic heart disease and mitral involvement, when there are apparently contradictory findings in the electrocardiogram and the roentgenogram regarding right ventricular enlargement.

Summary

The routine 12-lead electrocardiogram and additional right chest leads were studied in 63 persons having secondary R waves in right precordial leads and QRS duration less than 0.12 second. This group included 25 patients with congenital heart disease, 13 with acquired heart disease, and 25 with normal hearts.

A distinct pattern of abnormality was found in the majority of patients with heart disease, especially in those with congenital cardiac lesions. The accepted criteria for the diagnosis of incomplete right bundle-branch block were found in the majority of the normal subjects, and secondary R waves considered without apparent pathologic significance were found in many patients with heart disease and definite right ventricular hypertrophy.

Criteria based upon the following findings were of no value in differentiating secondary R waves in right precordial leads associated with heart disease from those not associated with heart disease: the QRS duration; time of inscription of the intrinsicoid deflection; greater amplitude of R′ compared with R without regard to the absolute height of R′; presence of slurring or notching of the QRS complexes; presence of a relatively broad S in leads I, V_5 and V_6; presence of secondary R wave or "abnormal" R′/S or R/Q ratio in aV_R; and the T-wave direction.

Reliable signs of an abnormal RSR pattern in right precordial leads were (1) A primary R wave higher than accepted normal range values for the involved age group, regardless of the amplitude of the secondary R. In our series a primary R higher than 8 mm. in V_{3R} and V_1 was always abnormal. (2) A secondary R wave higher than 6 mm., regardless of the amplitude of the primary R. (3) An R′/S ratio more than 1.0 in any lead from the right side of the precordium.

On the basis of these criteria, a definite diagnosis of abnormality was possible in 20 (80 per cent) of the 25 patients with congenital heart disease and in 6 (46 per cent) of the 13 with acquired heart disease.

A pattern of small R, relatively deep S (R′/S ratio less than 1.0), and a small R′ (5 mm. or less) (rSr′ pattern) was present in practically all the normal subjects but also in a significant number of patients with heart disease, 5 (20 per cent) of the 25 with congenital heart disease and 7 (54 per cent) of the 13 with acquired heart disease, and a definite electrocardiographic diagnosis of abnormality was not possible in these patients with the usual precordial leads.

The secondary R wave disappeared when additional right lower chest leads were taken in all the normal subjects with an rSr′ pattern (relatively deep S with R′ less than 6 mm.) in right precordial leads; it persisted unchanged or occasionally changed to an abnormally large notched R in all the patients with heart disease. In the latter group these changes were independent of the amplitude of the R′ or of the RSR pattern.

The presence of an rSr′ pattern in V_1 or V_2, or both, but its absence in V_{3R}, or an R′ in V_2 larger by more than 1.0 mm. than the R′ in V_{3R}, suggested that the R′ represented a normal electrocardiographic variation and was not a manifestation of heart disease.

The use of additional right lower chest leads —specifically V_{3R} or V_1 2 interspaces below the usual levels—may help in the differential diagnosis of doubtful cases of so-called incomplete right bundle-branch block. A persistent R′ in lower leads probably indicates abnormal right ventricular conduction or right ventricular hypertrophy. Disappearance of secondary R waves in lower right chest leads and their increase in higher leads, seen in normal subjects, support the impression that these secondary waves may be due to physiologic late activation of muscle near the outflow tract of the right ventricle or more specifically of the crista supraventricularis. The depolarization of these basal zones is represented by the direction of the terminal portion of the QRS vector.

Summario in Interlingua

Le electrocardiogramma routinari a 12 derivationes e in plus derivationes dextero-thoracic esseva studiate in 63 personas qui habeva secundari undas R in derivationes dextero-precordial e un duration QRS de minus que 0,12 secundas. Le gruppo consisteva de 25 patientes con congenite morbo cardiac, 13 con acquirite morbo cardiac, e 25 con cordes normal.

Un distincte configuration de anormalitates esseva trovate in le majoritate del patientes con morbo cardiac, specialmente in le patientes con congenite lesiones del corde. Le acceptate criterios pro le diagnose de incomplete bloco de branca dextere esseva trovate in le majoritate del subjectos normal, e secundari

undas R—considerate como disproviste de apparente signification pathologic—esseva presente in multe patientes con morbo cardiac e definite hypertrophia dextero-ventricular.

Criterios basate super le sequente lista de datos esseva sin valor in le differentiation inter secundari undas R in derivationes dextero-precordial que esseva associate con morbo cardiac e illos que non esseva associate con morbo cardiac: Le duration de QRS; le tempore del inscription del deflexion intrinsicoide; augmento del amplitude de R′ in comparation con illo de R sin referentia al altor absolute de R′; presentia de dentation o de continuitate indistincte in le complexos QRS; presentia de un relativemente large S in le derivationes I, V_5 e V_6; presentia de secundari unda R o de un proportion "anormal" R′/S o R/Q in aV_R; e la direction del unda T.

Signos indicante fidelmente un anormalitate del patron RSR in derivationes dextero-precordial esseva: (1) Un primari unda R de altor in excesso del area de valores considerate como normal pro le gruppo de etate in question, sin reguardo al amplitude del unda R secundari. In nostre serie un R primari de plus que 8 mm de altor in V_{3R} e V_1 esseva semper anormal. (2) Un secundari unda R plus alte que 6 mm, sin reguardo al amplitude de R primari. (3) Un proportion R′/S de plus que 1,0 in non importa qual derivation al dextera del precordio.

Super le base de iste criterios, un definite diagnose de anormalitate esseva possibile in 20 del 25 patientes con congenite morbo cardiac (80 pro cento) e in 6 del 13 patientes con acquirite morbo cardiac (46 pro cento).

Un combination de micre R e relativemente profunde S, i.e. un proportion R′/S de minus que 1,0, e un micre R′ de 6 mm o minus (patrono rSr′) esseva presente in practicamente omne le subjectos normal sed etiam in un numero significative de patientes con morbo cardiac. Isto valeva pro 5 del 25 patientes con congenite morbo cardiac (20 pro cento) e pro 7 del 13 con acquirite morbo cardiac (54 pro cento), e un definite diagnose electrocardiographic del anormalitate non esseva possibile in iste patientes per medio del usual derivationes precordial.

Le secundari unda R dispareva quando derivationes additional ab le thorace dextero-inferior esseva obtenite in le casos del patientes qui habeva un patrono rSr′ (S relativemente profunde con R′ de minus que 6 mm) in le derivationes dextero-precordial; illo persisteva o, a vices, se alterava in un anormalmente grande R a dentation in omne le patientes con morbo cardiac. In iste ultime gruppo, le mentionate alterationes esseva independente del amplitude del R′ o del patrono RSR.

Le presentia de un patrono rSr′ in V_1 o V_2 o in ambes insimul con su absentia in V_{3r} o le presentia, in V_2, de un R′ que excede le R′ de V_{3R} per plus que 1,0 mm de largor suggereva que le R′ representava un normal variation electrocardiographic e non esseva un manifestation de morbo cardiac.

Le uso de derivationes additional ab le thorace dextero-inferior—specificamente le uso de V_{3R} o V_1 a 2 interspatios infra le nivellos usual—pote esser de adjuta in le diagnose differential de casos dubitose del si-appellate incomplete bloco del branca dextere. Un persistente R′ in derivationes inferior indice probabilemente un anormalitate del conduction dextero-ventricular o un hypertrophia dextero-ventricular. Le disparition de secundari undas R in derivationes ab le thorace dextero-inferior e le augmento de tal undas in derivationes superior, vidite in subjectos normal, supporta le impression que iste undas secundari es le effecto de un tardive activation physiologic del musculo in le vicinitate del tracto de efflux del ventriculo dextere o plus specificamente del crista supraventricular. Le dispolarisation de iste zonas basal es representate per le direction del portion terminal del vector QRS.

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An infusion of norepinephrine sufficient to raise the diastolic pressure 20 mm./Hg was found to be capable of differentiating the pansystolic murmur of mitral regurgitation, ventricular septal defect and tricuspid regurgitation. It produced no changes in the murmur of tricuspid regurgitation. The apical murmur of mitral regurgitation was increased. The tricuspid murmur of ventricular septal defect was also increased and the pulmonary component of the second sound was accentuated.

SHEPS

A Study of Renal Function in Orthostatic Hypotension

By ERLING KRUGE BRODWALL, M.D.

IN orthostatic hypotension a considerable fall in blood pressure and cardiac output occurs in the erect position. There is an idiopathic form, most frequent in males 40 to 70 years of age. Further, there are symptomatic forms perhaps most frequently found in diabetes with neurologic disturbances.

Studies of renal function in orthostatic hypotension revealed decreased urine secretion in the erect position.[1, 2] There were falls both in renal plasma flow and in glomerular filtration rate when subjects with orthostatic hypotension were tilted into oblique position. Brun and associates[3] and Werkö et al.[4] found even in subjects without orthostatic hypotension a fall both in plasma flow and in glomerular filtration rate during tilting. It is therefore difficult to determine whether these changes in renal function in orthostatic hypotension are due to the fall in blood pressure or are caused by other changes consequent to the altered position.

In subjects without orthostatic hypotension, Werkö's group found no difference between the extraction of paraamino hippuric acid in the recumbent and tilted positions. No studies appear to have been made on the extraction ratio in orthostatic hypotension. The special purpose of this study is to determine whether there is any fall in the extraction ratio during the hypotensive phase in subjects with orthostatic hypotension.

Material and Methods

Two cases have been studied. O.S. (no. 1, table 1) was a 50-year-old man with idiopathic orthostatic hypotension who for about 10 years had suffered syncopal tendencies in the standing position. In the recumbent position the blood pressure was approximately 125/80 mm. Hg, falling in the standing position to approximately 50/30 mm. Hg. There was no change in pulse rate on change of position.

From the University Clinic, Medical Department, Bergen, Norway. (Chief: Professor O. J. Broch.)

M.S. (no. 2, table 1) was a 60-year-old man with the symptomatic type of orthostatic hypotension. He had suffered from diabetes for 2 years. During the last 12 months he had been troubled by syncopal attacks in the standing position and signs of polyneuritis. The blood pressure was approximately 120/80 mm. Hg in the recumbent position, falling in the standing position to approximately 60/40 mm. Hg and there was no concomitant change in the pulse rate.

The glomerular filtration-rate (inulin-clearance) and the renal plasma flow (paraamino hippuric acid clearance) were measured in the recumbent position and after various degrees of tilting. Methodologically we followed the description of Goldring and Chasis.[5] The extraction ratios were obtained by catheterization of the right renal vein. The subjects were studied in the postabsorptive state. Values for glomerular filtration rate and renal plasma flow have been corrected to a body surface of 1.73 M.^{2}

Results and Discussion

The findings presented in table 1 show a fall both in plasma flow and in glomerular filtration rate. This, however, takes place only after a considerable fall in blood pressure and in the head-up oblique position of 25° and 30° respectively. There is no change in the extraction of paraamino hippuric acid in the hypotensive phase. This finding agrees with the observations of Van Slyke[6] in experimental shock in dogs. He found decreased extraction of paraamino hippuric acid only after protracted and considerable shock and not until reduction of the plasma flow to below 10 per cent of control values. In our studies we did not try to obtain extreme falls in blood pressure as the consequent syncopal tendency might conceivably cause extrarenal reactions which in turn might influence the renal function.

In case 2 we tried to keep the blood pressure unchanged on a low level during the second and third period, partly in order to determine the influence of positional changes alone, and partly to see whether the renal function was

Table 1

Renal Function in Two Cases of Orthostatic Hypotension

Case	Observation	Posture Degree of Tilt	Blood Pressure	Effective Renal Plasma Flow ml./min.	Total Renal Plasma Flow ml./min.	Glomerular Filtration Rate ml./min.	Effective Filtration Fraction	"True" Filtration Fraction	Extraction Ratio
1. O. S.	1	0	105/70	354	514	69	0.20	0.14	0.63
	2	15°	100/65	341	515	62	0.18	0.12	0.68
	3	25°	70/50	358	580	66	0.17	0.11	0.59
	4	30°	70-60/40-30	293	425	54	0.19	0.13	0.68
2. M. S.	1	0	115/80	560	608	88	0.16	0.14	0.95
	2	25°	85/60	460	480	63	0.14	0.13	0.96
	3	20-25°	85/60	580	586	79	0.16	0.13	0.99
	4	0	110/85	645	695	85	0.13	0.12	0.94

Effective filtration fraction: $\frac{\text{Glomerular filtration rate}}{\text{Effective renal plasma flow}}$

"True" filtration fraction: $\frac{\text{Glomerular filtration rate}}{\text{Total renal plasma flow}}$

stable during a fairly long period of unchanged low blood pressure. We did not succeed, however, in varying the oblique position to any notable degree without a simultaneous change in blood pressure.

The values in the third period, beginning after 20 minutes in the oblique position and covering 18 minutes, may indicate a return to normal of the renal function. It is not, however, justifiable to draw any definite conclusion on the basis of only 1 observation, and further study of the subject is required. We found no change in the filtration fraction in the hypotensive phase. Thus our results do not agree with the observations by Corcoran and associates,[1] who found a greater filtration fraction in the hypotensive phase. They presumed this increase in the filtration fraction to be caused by dilatation of the vasa afferentia.

The observations of Brun et al.[3] and Werkö et al.[4] indicate that in subjects without orthostatic hypotension there is a significant increase in the filtration fraction in the oblique position. This was considered to be a consequence of a constriction of the vasa efferentia. If our observations can be confirmed, it would mean that in orthostatic hypotension no regulating constriction by the vasa efferentia takes place in standing position after a fall in blood pressure. This is moreover likely, since there is a reduced ability to vasoconstriction in this condition.

Summary

Renal function studies have been carried out in both the recumbent and in the oblique position in 2 cases of orthostatic hypotension. In both cases a definite fall in plasma flow and glomerular filtration rate took place, but this occurred only after registration of a considerable fall in blood pressure.

The filtration fraction remains unchanged after the fall in blood pressure. The extraction ratio remains unchanged after a considerable fall in blood pressure.

The data may indicate that the renal function becomes normal if blood pressure is kept on a low level over a fairly long period. However, further observations are required before any definite conclusion may be drawn.

Summario in Interlingua

Studios del function renal esseva effectuate in position supin e oblique in 2 casos de hypotension orthostatic. In ambe casos un definite reduction del fluxo de plasma e del intensitate de filtration glomerular occurreva, sed solmente post que un considerabile reduction del tension de sanguine habeva essite registrate.

Le fraction de filtration remane inalterate post le reduction del tension de sanguine. Le proportion de extraction remane inalterate post un considerabile reduction del tension de sanguine.

Le datos indica possibilemente que le function renal deveni normal si le tension de sanguine es mantenite

a un basse nivello durante un satis longe periodo de tempore. Tamen, observationes additional es requirite ante que un conclusion definitive pote esser formulate.

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Michael Servetus

In Spain, in the land where above all other places the Church and the Inquisition were stifling inquiry, in Villanueva in Arragon, there was born in 1511 a man, afterwards known by the name of Michael Servetus. Fleeing early from the Inquisition and his native soil, wandering in many lands, studying many things, learning anatomy under Sylvius and Günther at Paris, where he might have sat perhaps on the same bench with Vesalius, his active mind devoured all the knowledge of the time. He was in turn jurist, astronomer, meteorologist, geographer and doctor, but above all other things, a theologian. He threw himself with zeal into medical studies, and acquired in them such a reputation that the Archbishop of Vienna made him his physician; but his real interest in such studies lay in his belief that the study of anatomy was one of the paths which lead to a knowledge of God. To know, said he, the spirit of God, we must know the spirit of man; and to truly know the spirit of man, we must know the structure and working of the body in which that spirit resides. This led him to introduce anatomical disquisitions into his theological works. . . .

Everyone knows how in 1553, on Oct. 27, he was burnt at the stake in Geneva at the bidding of Calvin, because he would not recant his religious faith. With him, or at the same time, there was burnt the whole edition of 1000 copies of his book, the *Restitutio*, with the exception of some few copies which had passed into the hands of friends.—Sir M. Foster. *Lectures on the History of Physiology.* London, Cambridge University Press, 1901.

Chronic Idiopathic Pericardial Effusion

With Special Reference to the Development of Constrictive Pericarditis

By JAMES SCHEUER, M.D.

Chronic idiopathic pericardial effusion is an unusual condition that causes severe congestive heart failure and may be an early stage in the development of constrictive pericarditis. A case is reported and some other cases from the literature are reviewed in order to present the clinical features and treatment of this condition.

CHRONIC idiopathic pericardial effusion is not usually mentioned as a precursor of constrictive pericarditis. It has been assumed that most cases are sequelae of tuberculosis, other pyogenic infections, trauma with hemopericardium, or neoplasm.[1] The purpose of this communication is to report a case of chronic pericardial effusion recently seen on the wards of the Mount Sinai Hospital, and to draw attention to a condition that should be recognized and treated early, because of the possibility of the subsequent development of constrictive pericarditis. Examination of our hospital records since 1937 failed to reveal any other such case recognized in this hospital during that period.

Case Presentation

M.C., a 49-year-old Negro woman was hospitalized in 1952 because of shortness of breath and edema of the ankles. At that time, there was mild hypertension, and an x-ray was suggestive of pericardial effusion (fig. 1). She responded well to treatment for congestive heart failure with digitalis and diuretics. The patient underwent hysterectomy in 1955 for uterine fibroids, at which time the chest x-ray findings were similar to those observed in 1952. She continued to receive digitalis but experienced increasing symptoms of congestive failure and was admitted to The Mount Sinai Hospital on February 20, 1957. Examination revealed a thin woman who could lie flat without discomfort. Funduscopic examination revealed arteriolar attenuation and arteriovenous nicking. The cervical veins were distended, and there was a positive hepatojugular reflux. There were dullness and bronchial breathing with a few fine rales at the base of the left lung. The maximum cardiac impulse was felt in the seventh intercostal space in the left midaxillary line, and the area of cardiac dullness extended 3 cm. to the right of the sternum. The heart sounds were of good quality, and there was a harsh apical systolic murmur. The second aortic sound was louder than the second pulmonic and a third heart sound was present. The abdomen was protruberant with the presence of shifting dullness and a fluid wave. A firm spleen tip extended 4 cm. beneath the right costal margin. There was 3+ pitting edema of the sacrum and legs. The blood pressure was 180/115 mm. Hg. The pulse was 100 per minute and regular and the temperature was 100.4 F. Laboratory examination revealed a hemoglobin of 13.2 Gm. per cent, and leukopenia ranging from 2,400 to 4,900 cells per mm.^{3} with a normal differential count. Platelets varied between 88,000 and 180,000 per mm.^{3} and the Westergren sedimentation rate was 3 mm. per hour. Urinalysis revealed 1 to 3+ proteinurea, but was otherwise negative. Blood sugar, urea nitrogen, electrolytes, and routine liver function tests were all within normal limits. Hemoglobin electrophoresis showed A and S hemoglobin, and numerous lupus erythematosus preparations were negative. Gastric and urine cultures for the tubercle bacillus were negative and a tuberculin skin test of 1:10,000 was positive. The venous pressure was 125 mm. of water and the arm-to-tongue circulation time was 25 seconds. X-ray examination of the chest showed a globular cardiac shadow similar to the one taken in 1952. Poor cardiac pulsations were noted during fluoroscopy. The electrocardiogram revealed normal sinus rhythm, wide notched P waves, a P-R interval of 0.21 second, and depressed S-T segments and diphasic T waves over the left precordium (fig. 2). A vectorcardiogram showed a pattern of left ventricular hypertrophy.

On March 12 and 14, pericardiocenteses by the subxiphoid approach yielded a total of 250 ml. of straw-colored fluid that was sterile on culture for tubercle bacilli and pyogenic organisms. Pneumopericardium was induced, and x-ray films revealed a pericardium of normal thickness without evidence of adhesions or neoplasm (fig. 3). The patient responded well to digitalis and diuretics and

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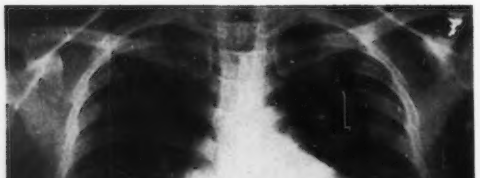

Figure 1

X-ray film taken in 1952 suggestive of pericardial effusion.

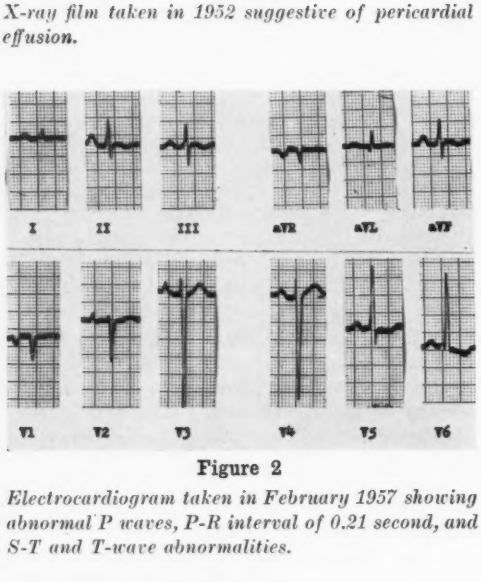

Figure 2

Electrocardiogram taken in February 1957 showing abnormal P waves, P-R interval of 0.21 second, and S-T and T-wave abnormalities.

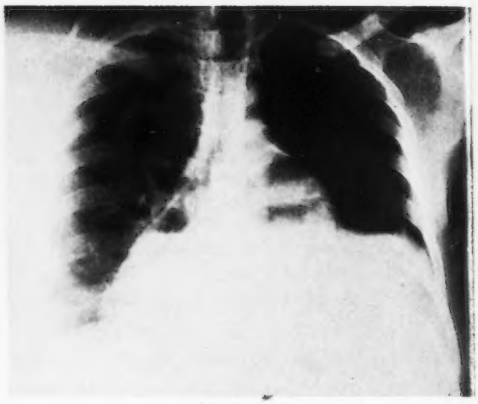

Figure 3

Pneumopericardium produced in March 1957 showing an air-fluid level and a thin pericardium.

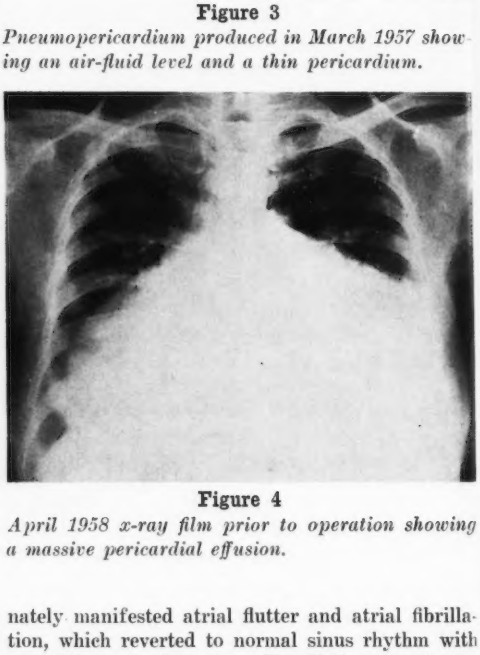

Figure 4

April 1958 x-ray film prior to operation showing a massive pericardial effusion.

was discharged June 1. Because of the recurrence of edema, she was readmitted October 30, at which time, except for greater hepatomegaly, the physical findings were unchanged. She again had a slight leukopenia, ranging from 3,800 to 6,400 cells per mm.^{3} The blood chemical and liver function tests were again normal. Venous pressure was 230 mm. and the circulation time was 33 seconds. There had been an increase in the size of the cardiac shadow on x-ray examination (fig. 4). On November 18 pericardiocentesis with pneumopericardium was performed, and x-ray films taken in the lateral decubitus positions showed a greatly enlarged heart. The fluid was bloody on this occasion, but was again sterile. During the admission, the patient had an unstable cardiac rhythm and alternately manifested atrial flutter and atrial fibrillation, which reverted to normal sinus rhythm with quinidine and digitalis. The P-R interval was then normal. The patient was discharged December 18, but had to be readmitted for congestive failure on May 5, 1958. Physical findings were unchanged, except that the blood pressures on this admission were usually around 140/90. Proteinuria was no longer present. Intradermal tests for blastomycosis, histoplasmosis, and coccidioidomycosis were negative. On June 17 the patient underwent a subtotal pericardiectomy, at which time a shaggy pericardium 2 to 4 mm. thick was resected from the anterior and lateral aspects of the heart. There was a large amount of pericardial fluid present and the heart was greatly enlarged. Postop-

atively the patient did well, and the venous pressure and circulation time returned to normal. Gross inspection of the pericardium showed congested tissue which in some areas had a shaggy fibrinous inner layer. The microscopic examination showed subacute fibrinous pericarditis. The patient was discharged without signs of congestive heart failure, and since operation has felt well while carrying on moderate activities. There has been no edema, but she has periods of dyspnea associated with weight gain every few weeks. These episodes have responded well to diuretics. A recent admission for further study revealed a radioactive iodine uptake of 43 per cent in 24 hours, and a protein-bound iodine of 4.9 μg. per cent. Right-sided heart catheterization demonstrated normal pressures in the right atrium, but elevated systolic pressures in the right ventricle and pulmonary artery to 65 mm. Hg with a pulmonary wedge pressure of 12 mm. Hg. The x-ray of the chest (fig. 5) showed a generally enlarged heart. Fluoroscopic and kymographic examinations showed good cardiac pulsations.

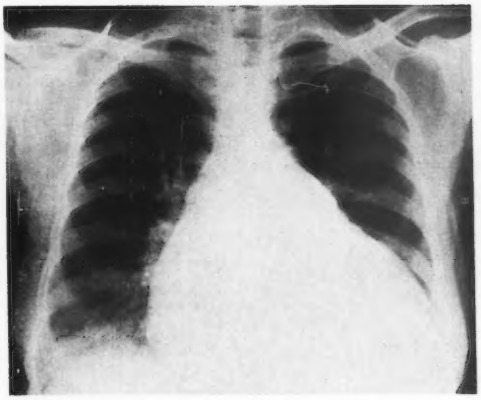

Figure 5

The x-ray film taken after the subtotal pericadiectomy and removal of all the pericardial effusion showing marked cardiomegaly.

Discussion

This is a case of chronic pericardial effusion lasting at least 6 years in a woman with asymptomatic hypertension, cardiomegaly, persistent right heart failure, and hepatosplenomegaly. She has a sickle-cell trait and a mild leukopenia, thrombocytopenia, and at times a mild anemia, the last 3 possibly secondary to hypersplenism. There was good response to pericardiectomy, although it is thought that in addition to her hypertension, a basic disease persists in her epicardium and myocardium.

Table 1 summarizes the findings reported in some other similar cases from the American literature. The data indicate that the disease occurs in patients over a wide age range, and in the limited sample here there is a 1 to 5 preponderance of male over female patients. Two cases occurred in siblings, and there is no indication whether there were infections or other environmental factors responsible. Cases have been followed for as long as 8 years. Usually symptoms or signs of congestive heart failure brought the patients to the physician, but 4 were discovered during examinations for other reasons. Cardiac findings were those frequently associated with pericardial effusion of any etiology. These were the presence of a third heart sound, paradoxical pulse, and massive right-sided heart failure.

There were no consistent laboratory aberrations other than those pertaining to the heart. The roentgenogram of the chest exhibited a large globular cardiac silhouette. Poor cardiac pulsations were consistently noted on fluoroscopy. When pneumopericardium was induced and x-rays were taken, the heart was usually found to be normal in size and the parietal pericardium was smooth and thin, without adhesions. Where electrocardiograms were recorded, most patients were found to be in normal sinus rhythm. However, wide-notched P waves were noted in several cases, and an unstable rhythm, shifting from normal sinus to atrial flutter or fibrillation, was present in 3. Low voltage QRS complexes were common and nonspecific S-T and T-wave changes were invariably present. Pericardiocentesis was performed frequently, usually yielding straw-colored fluid, which contained mononuclear cells or lymphocytes. In those patients in whom the protein content of the fluid was measured, it was between 5 and 7 Gm. per cent. Cardiomegaly was discovered by pneumopericardium, at postmortem examination, or at surgery in 6 cases, once associated with hypertension and twice with a large or-

Table 1

Case Reports	Age	Sex	Duration	Symptoms and Signs	Treatment
Barker and Johnson[2]	*18	m	6 yr.	Dyspnea, sinus rhythm, and later atrial fibrillation	Pericardiectomy
	38	m	5 yr.	Dyspnea, edema, sinus rhythm, and later atrial fibrillation	Pericardiectomy
	33	m	5 mo.	Dyspnea, edema, atrial fibrillation	Pericardiectomy
Mannix and Dennis[3]	41	m	7 mo.	Cough, night sweats, fever, dyspnea	Pericardiectomy
	43	f	5 mo.	Dyspnea, edema, BP 150/120	Pericardiectomy
	*67	m	2 yr.	Dyspnea, edema, low-grade fevers	Pericardiectomy
	*57	m	5 yr.	Dyspnea, cough, fever, edema	Pericardiectomy
	45	m	3 yr.	Congestive heart failure	Pericardiectomy
Contro, DeGiuli and Ragazzini[4]	7	f	4 yr.	Fever, cough, dyspnea at onset. Thereafter, asymptomatic	None
Goldner and Kroop[5]	44	m	about 1 yr.	Congestive heart failure	Partial pericardiectomy
Sanghvi and Samuel[6]	*19	m	7 mo.	Cough and dyspnea	None
Genecin (brothers)[7]	17	m	16 mo.	None	Pericardiectomy
	24	m	3 yr.	BP 140/90 to 190/100	None
Soloff and Zatuchni[8]	46	f	8 yr.	Dyspnea and fatigue	Cortisone
Yu et al.[9]	70	m	18 mo.	Dyspnea, palpitations, edema	Pericardiectomy
Ada et al.[10]	27	f	3 mo.	Dyspnea, fatigue, sticking chest pain	Surgery (type not specified)
Creech et al.[11]	*32	m	20 mo	Aching precordial pain and fullness in epigastrium	Pericardiectomy
Moe and Campos[12]	60	m	5 yr.	Chest pain, dyspnea, edema	None
Mount Sinai Hospital	49	f	6 yr.	Dyspnea, edema, hypertension sinus rhythm; later atrial flutter, fibrillation and sinus rhythm	Pericardiectomy

*Constrictive pericarditis.

Summary of Cases in American Literature

Pathology	Pericardial fluid Course		Miscellaneous
Constrictive pericarditis. Active chronic pericarditis	None examined	Progressive congestive heart failure. Died postoperatively	
Chronic fibrous pericarditis	Clear, straw colored	Progressive heart failure before and improvement after surgery	Cardiomegaly and thrombus in the right atrium at surgery
Chronic fibrous pericarditis, slightly thickened	Straw colored	Progressive heart failure before and improvement after surgery	Cardiomegaly and thrombus in the right atrium at surgery
3 mm. cartilaginous pericardium. Chronic fibrosing pericarditis	Straw colored	Recovery	3 years later, normal heart
3-4 mm. thick. Perivascular lymphocytes and hyalinized fibrin	Bloody (after many pericardiocenteses)	Recovery	
Constrictive pericarditis 5 mm. thick. Chronic fibrous pericarditis	None examined	Progressive heart failure before and improvement after surgery	
Constrictive pericarditis 4 mm. thick. Acute and chronic pericarditis	Blood-tinged fluid	Progressive heart failure before and improvement after surgery	
Subacute pericarditis	Clear, watery	Progressive heart failure before and improvement after surgery	
None	Light yellow. 5 Gm.% protein 10-15 lymphocytes per HPF	Asymptomatic	
Hyalinized connective tissue with some acute inflammation	Yellow, 5.98 Gm.% protein, no cells	Progressive heart failure before and improvement after surgery	Elevated PA, RV, and RA, and intrapericardial pressures
Granulation tissue. Chronic nonspecific pericarditis	Clear, straw colored	Increasing heart failure with decreasing heart size	Probable constrictive pericarditis
Chronic inflammation with cholesterol plaques	Yellow, cloudy 6.4 Gm.% protein Cholesterol 85 mg.%	Asymptomatic	Mild polycythemia
None	Brown fluid	Asymptomatic	Vascular anomalies in the eyegrounds
None	Serosanguineous	Improved on steroids	
Acute and chronic pericarditis, Granulation tissue, cholesterol deposits, foreign-body reaction	6.05 Gm.% protein 12 mg.% cholesterol. 6,900 WBC/mm.^{3} mostly lymphocytes	Increasing heart failure before and improvement after surgery	Heart enlarged at surgery. Catheterization at pericardiocenteses and postoperatively
Cholesterol plaques on visceral and parietal pericardium. Granulation tissue and foreign-body giant cells	1.020 specific gravity. 5.65 Gm.% protein. 120 mg.% cholesterol	Asymptomatic postoperatively	Serum cholesterol 167 mg.% Enlarged heart 7 years postoperatively
Yellow plaques and hyalinized connective tissue. Aggregates of lymphocytes and cholesterol clefts. Adherent pericardium	Yellow fluid 5.8 Gm.% protein 1.025 specific gravity. 263 mg.% cholesterol	Asymptomatic postoperatively	
Thickened fibrous wall. Cholesterol deposits. Shaggy visceral pericardium. 0.5-1.3 cm. Hyaline degeneration	Turbid yellow	Progressive heart failure resulting in death	Enlarged left ventricle
Shaggy pericardium 2-4 mm. thick. Subacute fibrinous pericarditis	Straw colored	Increasing heart failure before and less heart failure after surgery	Leukopenia and sickle trait. Marked cardiomegaly

ganized thrombus in the right atrium in patients who had atrial fibrillation.

Cardiac catheterization in 1 case[5] showed the typical early diastolic dip and plateau in the right ventricular tracing. There were elevated right heart diastolic pressures and an elevated intrapericardial pressure that fell after pericardiocentesis. The patient reported by Yu et al. was catheterized before and after pericardiectomy and showed an increase in stroke volume and a fall in atrial and venous pressures postoperatively, but had a persistently high pulmonary wedge pressure of 22 mm. Hg and pulmonary artery pressure of 47/20 mm. Hg. Also, in our case, there was pulmonary hypertension and a borderline pulmonary wedge pressure, which may be due to permanent vascular damage secondary to 6 years of passive congestion of the pulmonary vessels. Increased pulmonary venous pressure has been demonstrated in experimentally produced pericardial tamponade.[13]

Fourteen patients underwent partial or complete pericardiectomy and 12 of these improved considerably postoperatively. One patient who died hours after surgery had progressed to a stage of constrictive pericarditis and was moribund at the time of surgery.[2] One patient was treated with steroids and seemed to improve; however, the follow-up in this case was short. Pathologic reports, although usually brief, indicated that the pericardium usually measured between 1 and 4 mm. in thickness and on microscopic examination showed a chronic fibrous reaction. Of the 5 cases with true cardiomegaly, only ours had significant hypertension. Wood mentioned 6 cases with hypertension in which there were chronic pericardial effusions.[14] He suggested the possibility of a diminished aortic-coronary gradient in tamponade as a possible cause of chronic hypoxia and hypertrophy, and the increased oxygen extraction demonstrated by Yu may also be a reflection of diminished coronary flow. The 5 patients included in table 1 who had cholesterol either in the pericardium or in the effusion are included because they seem to differ in no other way from those without cholesterol, and they may not necessarily represent a separate entity. The mechanism of cholesterol deposition or formation in this chronic inflammatory situation is not well understood.[7] The 3 asymptomatic cases have been followed for periods of 13 months to 4 years without exhibiting congestive heart failure. Five cases with definite evidence of effusion were followed into a constrictive phase at which time surgery was performed in 4.

The diagnosis of chronic pericardial effusion must be recognized early in its course before severe hepatic damage or constrictive pericarditis occurs. It is during the stage of effusion that treatment is simple and effective. This condition should be suspected whenever predominantly right-sided congestive heart failure is associated with a large cardiac silhouette. The absence of typical findings of congenital, arteriosclerotic, or rheumatic heart disease should raise one's suspicion. The presence of muffled heart sounds, a diastolic third heart sound, a paradoxical pulse, Ewart's sign, low voltage of the QRS complex, and fluoroscopic or kymographic observation of diminished cardiac pulsation will make one investigate the diagnosis more fully. X-rays taken in the recumbent and lateral decubitus positions to observe changes in the cardiac silhouette, and the width of the mediastinal shadow may be useful. Angiocardiography, with either an opaque dye or carbon dioxide[8] will show the chamber size to be normal and the width from the chamber to the border of cardiac silhouette to be increased. If pericardial effusion is demonstrated, pericardiocentesis should be performed to learn the character of the fluid, its protein content, and to culture bacteria. The instillation of 150 to 200 ml. of air in the pericardial sac, after aspiration of fluid, with films taken in various positions will reveal the true heart size and contour, the presence of a tumor, or thickened or shaggy parietal pericardium. Pericardial biopsy is a valuable diagnostic procedure and will frequently give the etiologic diagnosis. This can be performed either with the closed,[6] or more

requently with the open technic.[15] With ither procedure, fluid is obtained at the same ime, but the latter method is also therapeutic, s a window is created between the pericardial avity and the left pleural space.

There are numerous diseases that cause hronic pericardial effusions and it is impor- ant to make an etiologic diagnosis if possible, or the treatment will be directed accordingly. Among the conditions that must be ruled out re tuberculous or mycotic infections, which re often discovered by culture and histologic study of the pericardium, myxedema, neo- plasm, periarteritis nodosa, lupus erythe- matosus,[1] scleroderma,[16] chylopericardium,[17] chinococcus cyst,[18] or postirradiation effu- sion.[19] Whether there is any relationship be- tween acute benign idiopathic pericarditis and chronic pericardial effusion is not clear. The cases reviewed in this paper may well repre- sent varied etiologies, but an attempt was made to rule out those mentioned above.

The course of this form of pericardial effu- sion is unpredictable. Patients may go on for long periods of time and be completely asymp- tomatic. In the cases reviewed, however, 5 went on to a constrictive phase, which led to difficult operations in some and death in at least 1 other. As the failure in chronic effu- sion is predominantly right sided, severe hepatic damage is to be anticipated, and in- deed a significant number of patients had ascites. Our patient had splenomegaly and evidence of hypersplenism. This situation must be relieved. The surgical treatment is well tolerated during the stage of effusion and usually consists of partial pericardiectomy, baring the anterior and lateral aspects of the heart. It has been thought that the creation of a window between the pericardium and pleu- al cavities might only be temporarily useful nd would eventually close, leaving the basic situation unchanged. Proudfit and Effler,[15] however, have created windows in 16 cases of pericardial effusion of various etiologies, some of which probably were similar to our patient, nd they reported remissions in 12. It is not known if any of their cases may have gone on to constrictive pericarditis postoperatively, as might be expected with the inflammatory membrane left in place. The finding of con- strictive pericarditis in 5 of the cases in this series seems an unusually high incidence. In- fectious and traumatic pericarditis are often associated with pericardial calcification, but there was no calcification reported in any of the cases reviewed. No etiology is found for a large portion of cases of constrictive pericar- ditis and it is possible that many go through an asymptomatic period of effusion. It cannot be predicted which cases of chronic pericar- dial effusion of unknown etiology will develop constrictive pericarditis. Therefore, it is sug- gested that all cases undergo pericardiectomy when the diagnosis is made.

Summary

A case of chronic idiopathic pericardial effusion in a middle-aged hypertensive woman is presented. The findings and course of 18 similar cases are reviewed. The course is un- predictable. Some patients will be asympto- matic. A significant percentage will develop adhesive or constrictive pericarditis, and others will have chronic tamponade with hepa- tosplenomegaly and ascites. The diagnosis, differential diagnosis, and treatment are dis- cussed.

It is concluded that since the course cannot be predicted, and since surgery provides a maximum therapeutic result when performed in the early stages, these cases should have a pericardiectomy when the condition is dis- covered.

Summario in Interlingua

Es presentate un caso de chronic idiopathic effusion myocardial, in que le patiente esseva un femina hyper- tensive de medie etate. Le constatationes e le curso clinic in 18 simile casos es revistate. Le curso es in- predicibile. Certe patientes es asymptomatic. Un pro- centage significative disveloppa adhesions o peri- carditis constrictive, e alteres ha tamponage con hepatomegalia e ascites. Es discutite le diagnose, le diagnose differential, e le tractamento del condition.

Le conclusion es que proque le curso non pote esser predicite e proque le intervention chirurgie produce un maximal effecto therapeutic quando illo es effec- tuate precocemente, pericardiectomia deberea esser executate in iste casos si tosto que le condition es discoperite.

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On Cardiac Murmurs

By Austin Flint, M.D.

In cases of considerable aortic insufficiency, the left ventricle is rapidly filled with blood flowing back from the aorta as well as from the auricle, before the auricular contraction takes place. The distension of the ventricle is such that the mitral curtains are brought into coaptation, and when the auricular contraction takes place the mitral direct current passing between the curtains throws them into vibration and gives rise to the characteristic blubbering murmur. The physical condition is in effect analogous to contraction of the mitral orifice from an adhesion of the curtains at their sides, the latter condition, as clinical observation abundantly proves, giving rise to a mitral direct murmur of a similar character.

A mitral direct murmur, then, may exist without mitral contraction and without any mitral lesions, provided there be aortic lesions involving considerable aortic regurgitation. —*Am. J. M. Sc.* n.s. **44**: 29, 1862.

Intracardiac Phonocardiography in Ventricular Septal Defect

By GEORGE A. FERUGLIO, M.D., AND RAMSAY W. GUNTON, M.D.

It has been demonstrated that intracardiac phonocardiography provides precise localization of the source of cardiovascular sounds. Can this technic be of practical help in the diagnosis of small or complicated ventricular septal defects? Is a ventricular septal defect ever silent? What mechanisms are responsible for the diastolic murmurs in ventricular septal defect? In an attempt to answer these problems, intracardiac phonocardiograms have been studied in 47 cases.

THE most useful clinical sign of ventricular septal defect is a loud, harsh, pansystolic murmur with maximal intensity over the midprecordium (Roger murmur).[1] This murmur is often accompanied by a mitral diastolic rumble, and by an early diastolic murmur at the base or along the left sternal border of uncertain origin.[2] This typical auscultatory picture may be greatly altered when ventricular septal defect is associated with high pulmonary vascular resistance, pulmonary stenosis, overriding aorta, or aortic insufficiency. The role of the septal defect in the production of sounds in these conditions, cannot be established by simple auscultation or ordinary chest phonocardiography.

Previous experience has demonstrated that intracardiac phonocardiography[3-5] provides precise localization of the source of cardiovascular sound. The practical value of this information has been shown in particular in ventricular septal defect in which the intracardiac phonocardiogram is of diagnostic value[5-9] even in the presence of equivocal catheterization and dye-dilution studies,[10] by localizing a Roger murmur within the right ventricle.

It is the purpose of this paper to present the intracardiac phonocardiographic findings in 47 proved cases of ventricular septal defect and to emphasize the value of intracardiac phonocardiography not only in establishing the diagnosis of ventricular septal defect, but also in clarifying the site and mechanism of the basal and apical diastolic murmurs and the role of the interventricular communication in complicated ventricular septal defect.

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Material and Methods

The 47 patients included in this study ranged in age from 8 to 43 years, the majority being in the second decade. There were 20 male and 27 female subjects. Right heart catheterization was done in all patients. The study included calculation of systemic and pulmonary blood flows and recording of indicator-dilution curves from multiple sites. In 12 cases the septal defect was crossed and in 8 the aorta was catheterized. In addition, 26 patients had selective biplane angiocardiography at a speed of 1 to 12 frames per second. Twelve had corrective surgery with use of cardiopulmonary bypass and 4 were examined post mortem.

The cases have been grouped as in table 1.

Table 1

Diagnoses in Forty-seven Cases of Ventricular Septal Defect

Diagnosis	Number of cases
Uncomplicated ventricular septal defect*	18
Ventricular septal defect with aortic insufficiency	2
Ventricular septal defect with pulmonary hypertension	10
Ventricular septal defect with pulmonary stenosis (normal aortic root and normal peripheral arterial oxygen saturation)	3
Tetralogy of Fallot	14

*Two cases in this group had complete atrioventricular block and 1 case was of traumatic origin.

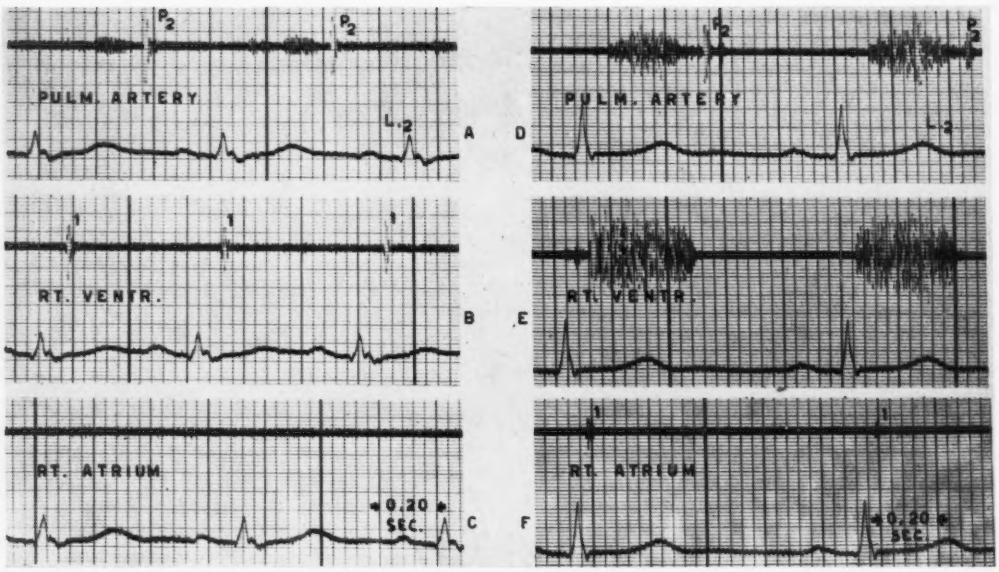

Figure 1

Intracardiac phonocardiograms in a normal subject and in a patient with ventricular septal defect. In the normal subject (left) *note,* A, *the short systolic flow murmur in the pulmonary artery;* B, *the absence of murmurs in the right ventricle;* C, *the absence of murmurs and sounds in the right atrium. In the patient with ventricular septal defect* (right) *note,* D, *the intense flow murmur in the pulmonary artery;* E, *the loud pansystolic murmur in the right ventricle;* F, *the absence of murmurs in the right atrium.*

Intracardiac sounds were recorded by means of the sound catheter originally described by Lewis et al.[3] The intracardiac microphone is a hollow cylinder of activated barium titanate incorporated in the tip of a specially designed catheter which is approximately the size of a no. 5 Cournand catheter. The output of the microphone after preliminary amplification by a 3-stage transistorized pre-amplifier** was fed into a 2-channel photographic recorder used for routine clinical phonocardiography. All records were made at the paper speed of 75 mm. per second. The phonocatheter was introduced under fluoroscopic guidance following routine cardiac catheterization. During the latter procedure reference marks were placed on the fluoroscopic screen to locate the pulmonic and tricuspid orifices. Simultaneous intracardiac and external sound recordings were also obtained.

**Phonocatheters and pre-amplifiers were built and made available to the authors by the Naval Air Development Center of Johnsville, Pennsylvania.

Results

Uncomplicated Ventricular Septal Defect

Of the 18 cases with uncomplicated ventricular septal defect, 7 had rather small defects and a pulmonary blood flow less than twice the systemic; 11 had large left-to-right shunts with a pulmonary blood flow 2 to 3 times the systemic flow. In the latter group of 11 patients were 2 cases of complete atrioventricular block. In the former group there was 1 case of traumatic origin.

The most striking intracardiac phonocardiographic feature in all, compared to normal subjects, was a loud, harsh, pansystolic murmur within the right ventricle (fig. 1). This murmur was usually loudest in the outflow tract of the ventricle and decreased toward the apex. In the case of the traumatic defect (fig. 2), however, in which the opening was localized by the course of the catheter

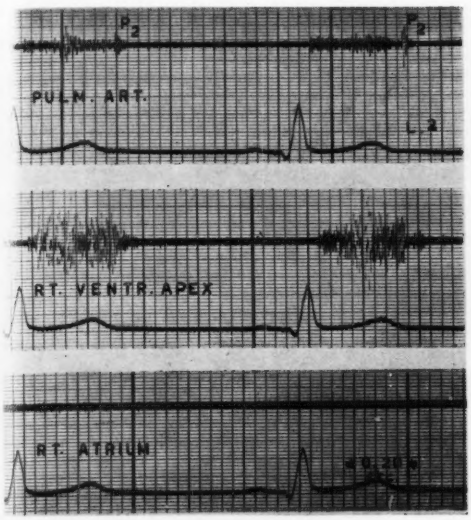

Figure 2

Intracardiac phonocardiogram in a patient with traumatic ventricular septal defect. Note the loud pansystolic murmur recorded near the apex of the right ventricle and the flow murmur in the pulmonary artery.

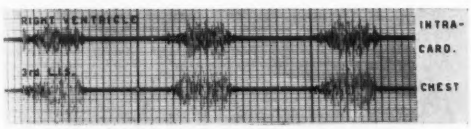

Figure 3

Simultaneous intracardiac phonocardiogram from the right ventricle and chest phonocardiogram in a case of ventricular septal defect. Note the similarity in the character and duration of the murmur.

In the lower third of the septum, the murmur was loudest in the apical region.

The intraventricular murmur recorded by the sound catheter had the characteristics of that recorded simultaneously over the midprecordium (fig. 3). It started with the first sound, lasted throughout systole and was composed of vibrations of varying frequency and intensity. This murmur disappeared suddenly when the sound catheter was withdrawn into the right atrium where, as in normal subjects, either a rudimentary first and second sound were recorded or no sounds at all (fig. 1).

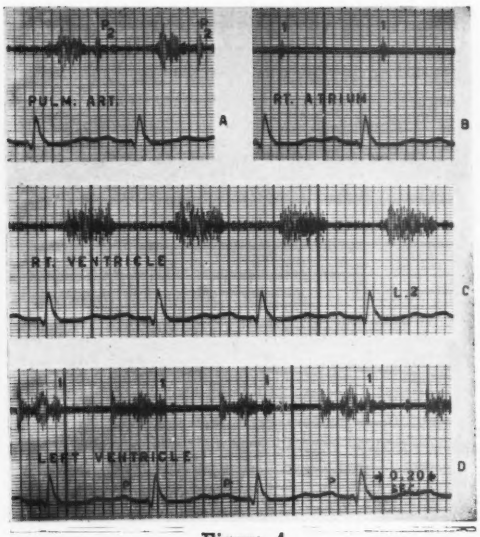

Figure 4

Intracardiac phonocardiogram in ventricular septal defect with large left-to-right shunt. Note, A, *flow murmur in the pulmonary artery;* B, *absence of murmurs in the right atrium;* C, *pansystolic murmur in the right ventricle;* D, *middiastolic murmur with presystolic accentuation in the left ventricle due to increased flow across the mitral valve.*

Within the pulmonary artery, a flow murmur louder than that usually recorded in normal subjects (fig. 1) was observed. The pulmonary valve closure was of normal intensity or slightly accentuated.

An early diastolic murmur was recorded in the upper outflow tract of the right ventricle just beneath the pulmonary valve, in only 1 of the 11 cases with large left-to-right shunt.

In 3 patients with large left-to-right shunt in whom an apical diastolic rumble was present on auscultation, the sound catheter was passed across the defect into the left ventricle. In this chamber no systolic murmur was recorded. There was a long diastolic murmur with the characteristics of a mitral murmur: low-pitched, "decrescendo" in middiastole, with presystolic accentuation (fig. 4*D*).

In the 2 cases with complete atrioventricular block and large left-to-right shunt, the intracardiac phonocardiographic features were

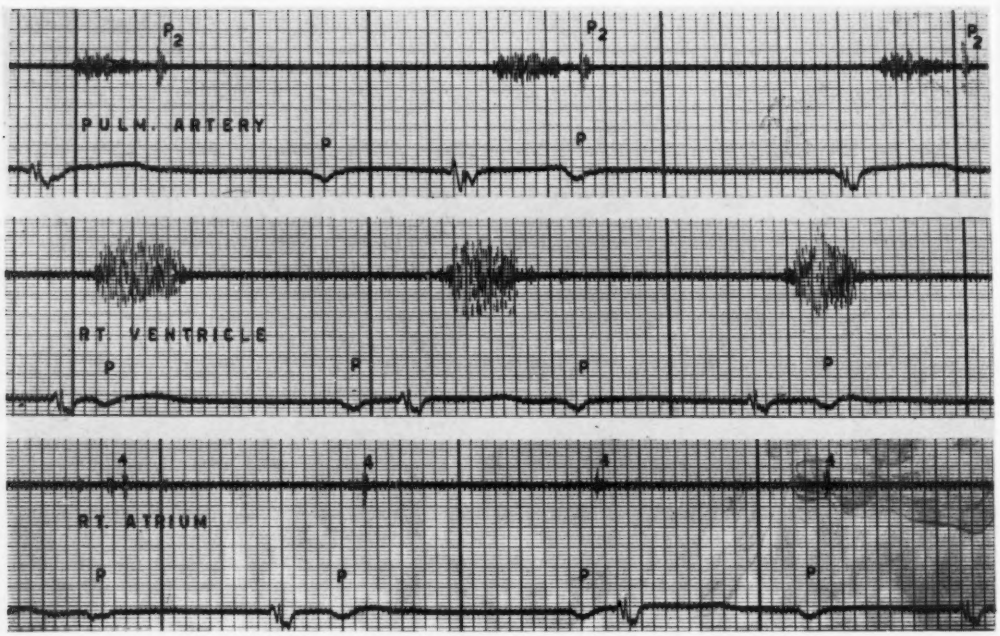

Figure 5

Intracardiac phonocardiogram in ventricular septal defect with complete atrioventricular block. There is a flow murmur in the pulmonary artery and a pansystolic murmur in the right ventricle. Note the absence of a diastolic murmur in the right ventricle and the presence of atrial sounds in the right atrium.

those encountered in the majority of uncomplicated ventricular septal defects. In the right atrium, however, an atrial sound followed each P wave of the electrocardiogram (fig. 5).

Ventricular Septal Defect with Aortic Insufficiency

The 2 patients with ventricular septal defect and aortic insufficiency proved by retrograde aortography, had on clinical auscultation and external phonocardiography a continuous murmur, which could not be differentiated from that of a patent ductus arteriosus, aortic septal defect, or ruptured sinus of Valsalva (fig. 6). In these cases, the correct diagnosis could not be established by routine heart catheterization.

The intracardiac phonocardiogram (fig. 6) showed a loud pansystolic murmur within the right ventricle as in isolated ventricular septal defect and no diastolic murmur. In the pulmonary artery a midsystolic murmur and a loud pulmonary second sound were recorded. There were no unusual findings in the right atrium.

On the basis of the absence of a continuous murmur within the pulmonary artery,[3–7] the diagnoses of patent ductus arteriosus and aortic septal defect were excluded. The possibility of rupture of a sinus of Valsalva into the right ventricle or right atrium could also be excluded because of the absence of a continuous murmur in these chambers.[7]

Ventricular Septal Defect with Pulmonary Hypertension

Ten patients with ventricular septal defect had a pulmonary systolic arterial pressure greater than twice the normal value. Of these, 7 had a small left-to-right shunt and 3 had a large left-to-right shunt with a pulmonary blood flow 2 to 3 times the systemic flow. In all patients a systolic murmur was recorded within the right ventricle. This murmur was

extremely loud occupying all systole, in the 3 cases with large left-to-right shunt; it was very soft and limited to the first part of systole in the 7 cases with small left-to-right shunts (fig. 7). A comparable difference in intensity was noted in the mid-systolic murmur recorded within the pulmonary artery; this murmur having less intensity with smaller pulmonary blood flow. Features common to both groups were an early diastolic murmur within the outflow tract of the right ventricle and a loud pulmonary second sound in the pulmonary artery. On auscultation an early blowing diastolic murmur had been heard in the second and third left intercostal spaces along the sternal border in 8 patients. No abnormal features were noted within the right atrium.

Ventricular Septal Defect with Pulmonary Stenosis

Three patients in addition to a ventricular septal defect had a pressure gradient of 50 mm. Hg or more across the pulmonary valve, a pulmonary blood flow up to 3 times the systemic flow, a normal aortic root, and normal peripheral arterial oxygen saturation.

The intracardiac phonocardiogram (fig. 8) from within the pulmonary artery, showed a midsystolic murmur of great intensity and a soft, delayed pulmonary second sound. These findings are similar to those observed within the pulmonary artery in cases of isolated pulmonary stenosis (fig. 8*A*).

In the right ventricle a loud pansystolic murmur was constantly present in cases of ventricular septal defect with pulmonary stenosis falling in this group (fig. 8*E*); it was absent in cases of isolated pulmonary stenosis (fig. 8*B*). No abnormal findings were observed within the right atrium in this group.

Tetralogy of Fallot

Fourteen patients had in addition to an interventricular communication, the other characteristic features of Fallot's tetralogy: severe pulmonary stenosis and overriding aorta. In all, the left-to-right shunt was insignificant and there was peripheral arterial oxygen unsaturation. The intracardiac phonocardiogram in these cases (fig. 9) revealed a loud diamond-shaped murmur within the pulmonary artery and a very soft and delayed pulmonary second sound occurring 0.08 to 0.12 second after the aortic second sound. No murmurs were recorded within the right ventricle in 8 patients; in 6 an early soft systolic murmur was observed. Within the aorta an early, usually soft systolic murmur and a loud aortic second sound were recorded.

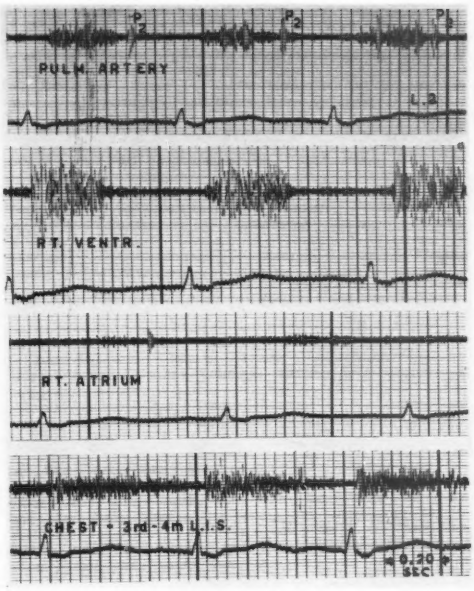

Figure 6

Intracardiac and external phonocardiograms in a case of ventricular septal defect with aortic insufficiency. There is a continuous murmur on the chest but only a systolic murmur in the pulmonary artery, excluding patent ductus arteriosus and aortic septal defect. There is only a pansystolic murmur in the right ventricle, excluding rupture of a sinus of Valsalva into this chamber.

Discussion

A loud pansystolic murmur sharply localized within the right ventricle and usually loudest in the outflow tract of this chamber, is a constant sign in uncomplicated ventricular septal defect. It corresponds in shape and duration to the murmur recorded externally from the third and fourth left intercostal

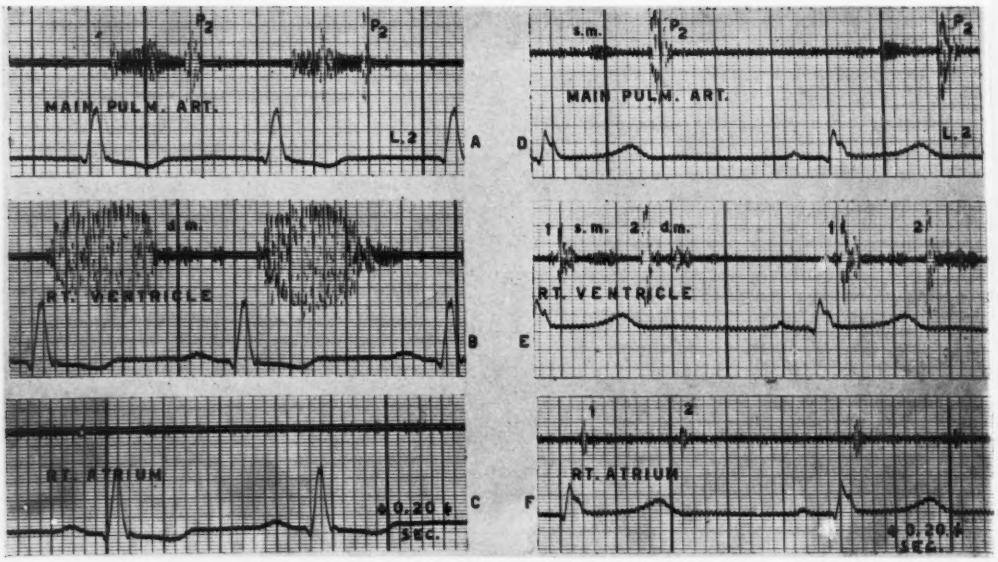

Figure 7

Intracardiac phonocardiogram in ventricular septal defect with pulmonary hypertension. Note that with large left-to-right shunt (left) *there is in* A *the usual flow murmur in the pulmonary artery followed by a loud second sound. In* B *a loud pansystolic murmur in the ventricle followed by an early diastolic murmur. With small left-to-right shunt* (right) *note in* D, *the less intense flow murmur in the pulmonary artery and a loud pulmonary closure; in* E, *a short soft systolic murmur and an early diastolic murmur in the right ventricle.*

spaces and described in detail by Roger 80 years ago.[1] Although by auscultation and chest phonocardiography the murmur may be present over a large precordial area, when recorded by the phonocatheter it is localized in the ventricular chamber and disappears dramatically when the catheter is withdrawn into the right atrium or advanced into the pulmonary artery. It is because of this precise localization that intracardiac phonocardiography is of exceptional value in the diagnosis of ventricular septal defect.

The intensity of the intracardiac murmur is not related to the size of the defect in isolated ventricular septal defect. It is this fact which makes intracardiac phonocardiography the technic of choice in the diagnosis of small defects with shunts less than 0.5 L./min. in which blood oxygen determinations fail to establish the presence of an interventricular communication.[11] A small ventricular septal defect is one possibility to be considered in the differential diagnosis of an "innocent left parasternal murmur."[11]

Errors in the diagnosis of ventricular septal defect from oxygen saturation studies are not infrequent and may be avoided with the help of intracardiac phonocardiography. It is known[2, 12] that depending on the position of the septal defect, the jet of arterial blood from the left ventricle may enter either the tricuspid or the pulmonary valve, yielding a misleading oxygen rise in the atrial or pulmonary blood samples. In this situation a ventricular septal defect may be overlooked on the basis of the oxygen studies alone.

In other conditions, low-lying atrial septal defect or large patent ductus arteriosus with pulmonary incompetence, a significant oxygen rise may be detected in the right ventricle suggesting interventricular communication which is in fact not present. In this case the

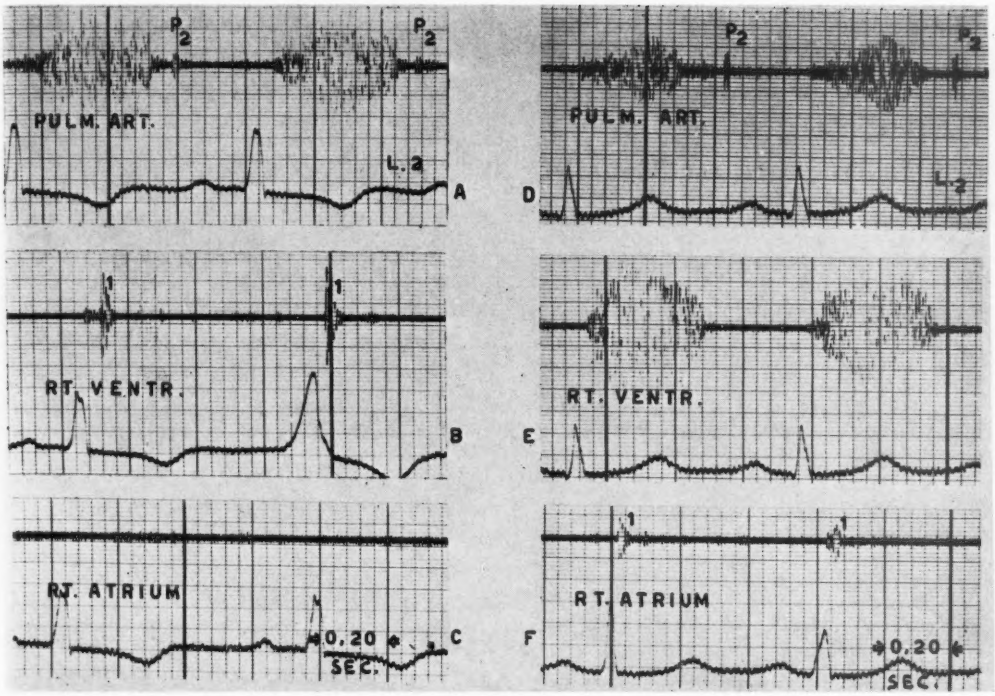

Figure 8

Intracardiac phonocardiograms in 2 subjects with pulmonary stenosis: one with intact ventricular septum (left), *the other with ventricular septal defect and left-to-right shunt* (right). *Note in each subject, in the pulmonary artery* (A *and* D) *the diamond-shaped murmur of pulmonary stenosis, and a soft, delayed pulmonary closure. In* B *the silent right ventricle in the absence of ventricular septal defect is contrasted in* E *with the loud pansystolic murmur of ventricular septal defect.*

intracardiac phonocardiogram from the right ventricle will reveal no systolic murmur and will exclude ventricular septal defect.

The combination of ventricular septal defect with aortic insufficiency, congenital or acquired, is not rare. It was reported to be present in 5 per cent of cases in a recent series of ventricular septal defects.[13] This combination may be mistaken clinically and at catheterization for patent ductus arteriosus, aortic septal defect, or ruptured aneurysm of a sinus of Valsalva into the right ventricle. Thoracotomy has been performed in error because of the incorrect diagnosis of patent ductus arteriosus.[14] The differential diagnosis is simplified by intracardiac phonocardiography. In cases of ventricular septal defect with aortic insufficiency there will be a typical Roger murmur in the right ventricle; in cases of patent ductus arteriosus or ruptured sinus of Valsalva into the right ventricle there will be a continuous machinery murmur within the pulmonary artery or the right ventricle respectively.[2, 5, 6]

When ventricular septal defect is complicated by high pulmonary vascular resistance or pulmonary stenosis, the intensity of the systolic murmur in the right ventricle decreases proportionally to the left-to-right shunt. The murmur also becomes shorter and may be present only in one part of systole. It never disappears. In the presence of large left-to-right even with elevated pulmonary arterial pressure, a very loud pansystolic mur-

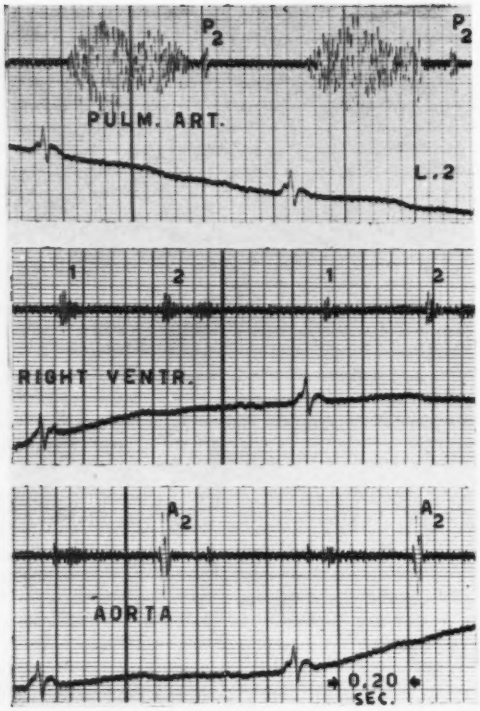

Figure 9

Intracardiac phonocardiogram in a subject with severe tetralogy of Fallot. There is a loud ejection type of murmur in the pulmonary artery and a delayed soft pulmonary valve closure. The right ventricle is silent, despite the proved presence of the ventricular septal defect, due to the absence of left-to-right shunt across the defect. There is a soft systolic murmur within the aorta and a prominent aortic valve closure.

mur is to be expected in the right ventricle. This sign is of great importance in the differential diagnosis between ventricular septal defect with pulmonary hypertension and patent ductus arteriosus with pulmonary hypertension plus pulmonary valvular insufficiency. This diagnostic problem was stressed in a recent report[15] in which 10 surgically proved cases of patent ductus arteriosus simulated so closely ventricular septal defect that surgical correction by extracorporeal circulation was initially considered for each of the patients and was attempted in 2.

Only in cases of severe tetralogy of Fallot is a systolic murmur absent in the right ventricle, despite the presence of ventricular septal defect. In this condition because of the equal pressure in the ventricles and the overriding aorta "blood does not flow from one ventricle to the other but from both ventricles into the aorta."[16] The ventricular septal defect is silent as already suggested[17, 18] and the pulmonary stenosis is responsible alone for the harsh systolic murmur heard over the mid-precordium.[19]

With respect to the early basal diastolic murmur in ventricular septal defect, 3 possible mechanisms may be suggested: pulmonary insufficiency, aortic insufficiency, and flow across the defect.[2] It seems unlikely that flow across the defect is responsible for such a diastolic murmur. It was not observed in the right ventricular phonocardiograms of the 2 cases in this series, with complete atrioventricular block and large pulmonary blood flow in which the very prolonged diastole should have created the best hemodynamic conditions for an interventricular shunt. Both aortic and pulmonary insufficiency may be responsible for the early basal diastolic murmur in ventricular septal defect. Intracardiac phonocardiography permits differentiation of the aortic from the pulmonary diastolic murmur because only the latter is recorded in the outflow tract of the right ventricle. No diastolic murmur was observed in this chamber in the cases of ventricular septal defect with aortic insufficiency included in this series.

A diastolic murmur of functional pulmonary incompetence was recorded in all cases of ventricular septal defect with pulmonary hypertension, whether the left-to-right shunt was large or small. Such a murmur was recorded only once in uncomplicated ventricular septal defect. In this case the left-to-right shunt was large and pulmonary blood flow was over 3 times the systemic flow. One may conclude that with the exception of the cases in which aortic insufficiency is present, an early diastolic murmur in ventricular septal defect is indicative either of high pulmonary vascu-

r resistance or high pulmonary blood flow.

The mitral origin of the apical diastolic urmur in ventricular septal defect, first described by Laubry and Pezzi in 1921[20] has en confirmed beyond doubt by the sound atheter, which demonstrated such a murmur ithin the inflow tract of the left ventricle ust beneath the mitral valve. A similar murur due to increased flow across the mitral alve has been recorded in other conditions ich as tricuspid atresia.[21]

Summary

Intracardiac phonocardiograms, with use of a barium titanate microphone, have been recorded in 47 proved cases of ventricular septal defect.

A loud pansystolic murmur localized within the right ventricle is a diagnostic sign of uncomplicated ventricular septal defect, even when clinical and catheterization findings are equivocal.

In ventricular septal defect complicated by pulmonary hypertension or pulmonary stenosis, the murmur is always present with left-to-right shunt and is proportional in duration and intensity to the volume of the shunt.

In severe tetralogy of Fallot with no left-to-right shunt, the ventricular septal defect is silent.

Intracardiac phonocardiography permits the differential diagnosis of ventricular septal defect with aortic insufficiency, from patent ductus arteriosus, aortic septal defect, and rupture of a sinus of Valsalva.

The mitral origin of the apical diastolic murmur in ventricular septal defect has been confirmed.

Evidence supports the view that the early diastolic murmur in ventricular septal defect does not rise from the defect itself but from pulmonary valvular insufficiency.

Summario in Interlingua

Per medio de microphonos a titanato de barium, phonocardiogrammas intracardiac esseva registrate in 47 provate casos de defecto ventriculo-septal.

Un forte murmure pansystolic, locate intra le ventriculo dextere, es un signo diagnostic de non-complicate defecto ventriculo-septal, mesmo quando le constatationes clinic e catheteric es equivoc.

In casos de defecto ventriculo-septal complicate per hypertension pulmonar o stenosis pulmonar, le murmure es semper presente con un shunting sinistro-dextere e es proportional in duration e intensitate al volumine del shunting.

In sever tetralogia de Fallot sin shunting sinistro-dextere, le defecto ventriculo-septal es silente.

Phonocardiographia intracardiac permitte le diagnose differential de defecto ventriculo-septal con insufficientia aortic contra patente ducto arteriose, defecto aorto-septal, e ruptura del sino de Valsalva.

Le origine mitral del diastolic murmure apical in defecto ventriculo-septal esseva confirmate.

Es presentate datos que supporta le conception que le murmure eodiastolic in defecto ventriculo-septal ha su origine non in le defecto mesme sed in insufficientia pulmono-valvular.

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Kellaway, G: Rupture of the Interventricular Septum as a Complication of Myocardial Infarction. Scottish M.J. **4**: 310 (June), 1959.

Four case reports of rupture of the infarcted ventricular septum are presented. The incidence of this complication was 0.5 per cent among all hospitalizations for myocardial infarctions during 1954-1958. The patients were elderly, ranging from 65 to 84 years. In each instance a characteristic harsh pansystolic apical or lower left sternal area murmur and thrill were detected within 1 week following the onset of a first myocardial infarction, and each patient then developed fatal hypotension and heart failure. The infarction was extensive in all cases and was located anteroseptally (with electrocardiographic Q_{V1}-V_6) in 3 and posteroseptally in 1. The diameter of the perforation was 5 mm., 12 mm., and 12.5 mm. in the 3 autopsied cases. The first of these had become occluded by thrombus and had cardiac catheterizations been done under such circumstances, the septal perforation would not have been detected since there would have been no shunt. The high mortality rate on medical treatment, 87 per cent within 8 weeks, led the authors to view favorably the possibilities offered by surgical closure of the perforation.

ROGERS

Configuration of Elastic Tissue of Pulmonary Trunk in Idiopathic Pulmonary Hypertension

By DONALD HEATH, M.D., AND JESSE E. EDWARDS, M.D.

A study was made of the configuration of the elastic tissue of the pulmonary trunk in 6 cases of idiopathic pulmonary hypertension. The ages of the patients ranged from 12 to 54 years. The pattern was that of the adult pulmonary type in the 5 female patients, whereas it more closely resembled the fetal, aorta-like type in the single male patient. These data are interpreted as indicating that idiopathic pulmonary hypertension is acquired in most cases but that it may be present from birth in a minority of instances.

THE characteristic clinical history of patients who have idiopathic pulmonary hypertension suggests that it is acquired in childhood or early adult life. Most patients with this disease live normal lives before the development of intractable pulmonary hypertension and congestive cardiac failure, which usually lead to death within 3 years or so.[1] Berthrong and Cochran,[2] however, found that 2 of their patients with this disease who also had a small patency of the foramen ovale were cyanotic from birth, suggesting that the pulmonary vascular resistance had been abnormally increased from birth. Study of the histologic structure of the pulmonary trunk in such cases may shed some light on this problem, for recent work suggests that the configuration of the elastic tissue of this artery depends on whether pulmonary hypertension is present from birth or develops later in life.[3] This communication describes the microscopic structure of the elastica of the pulmonary trunk in 6 proved cases of idiopathic pulmonary hypertension and discusses the significance of the results.

Material and Methods

Six patients who had idiopathic pulmonary hypertension were included in the study. All of these patients showed the clinical, roentgenologic, and electrocardiographic features characteristic of severe pulmonary hypertension, and it was subsequently demonstrated at necropsy in each instance that congenital cardiac anomalies were not present. The cases fulfill the criteria generally accepted as necessary for the diagnosis of "primary pulmonary hypertension." Five patients (cases 1 to 5) were female, their ages being 12, 21, 30, 36, and 54 years, respectively; the other patient (case 6) was a 23-year-old man. Cardiac catheterization had been performed in cases 3 and 6, and the results of this investigation are shown in table 1. In each case, the diagnosis was confirmed at necropsy. All patients had dilatation and hypertrophy of the right ventricle, dilatation of the right atrium, pulmonary-valve ring, and pulmonary trunk, and atherosclerosis of the pulmonary arteries.

Transverse blocks of the pulmonary trunk and the aorta were removed from sites 2 cm. above the respective valves and were embedded in paraffin. Histologic sections were prepared and stained by Verhoeff's method to demonstrate the elastic tissue; van Gieson's counterstain was employed. A histologic study of the configuration of the elastic tissue in both vessels was made; in each instance, the tissue of the pulmonary trunk was designated as "aortic" or "adult pulmonary" in type. This classification is based on the following data. In the fetus, the configuration of the elastic tissue in the media of the pulmonary trunk (fig. 1*a*) is similar to that of the aorta (fig. 1*b*), although minor differences are present. Both vessels contain many elastic fibrils among the smooth muscle and collagen. These fibrils are long, uniform, crenated, and tightly packed, and are parallel with one another. Although this configuration of elastic tissue remains in the adult aorta (fig. 1*c*), changes occur in the normal pulmonary artery, so that the adult appearance is one of a loosely arranged network of branching, irregularly shaped, fragmented elastic fibrils (fig. 1*d*). A transitional pattern is found in infancy. In severe pulmonary hypertension, the media of the elastic pulmonary artery thickens in all cases, but the configuration of the

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Table 1

*Cardiac-Catheterization Data in Two Cases of Pulmonary Hypertension**

Case	Arterial blood pressure, mm. Hg: Pulmonary Mean	Pulmonary Pulse	Radial Mean	Radial Pulse	Index of pulmonary blood flow, L./min./m.^{2}	Total pulmonary resistance, dynes sec. cm.$^{-5}$	Ratio of pulmonary to systemic resistance
3	66	42	90	36	1.9	1550	0.7
6	70	44	65	49	2.1	1300	0.9

*We are indebted to Dr. E. H. Wood, Section of Physiology, Mayo Clinic, for these data.

elastic tissue is related to the type of underlying disease. In cases of large ventricular septal defect or widely patent ductus arteriosus, wherein pulmonary hypertension is present from birth, the media of the pulmonary artery retains the fetal relationship to the aorta and has an elastic configuration similar to that of the aorta. In atrial septal defect of the foramen-ovale type or mitral stenosis of rheumatic origin, wherein pulmonary hypertension is acquired, the configuration of elastic tissue in the media of the pulmonary artery is like that of the adult pulmonary vessel.

A previous study[3] of the histologic structure of the pulmonary trunk at different ages in 71 control cases, in 44 cases of congenital heart disease with pulmonary hypertension, and in 31 cases of congenital heart disease with pulmonary stenosis should be consulted for a detailed description and a discussion of the significance of the various configurations of elastic tissue that may be found in the pulmonary trunk of such patients.

Results

In cases 1 to 5, the configuration of elastic tissue in the pulmonary trunk was of the adult pattern (fig. 2*a-e*). It was indeterminate in case 6 but resembled the fetal, aorta-like pattern more than it did the adult pulmonary configuration (fig. 2*f*). In all instances, the configuration of the aorta was normal.

Comment

It has been shown previously[3] that a difference exists between the configuration of the elastic tissue of the pulmonary trunk in the group of patients with a free communication between the systemic and pulmonary circulations from birth, such as a large ventricular septal defect or a widely patent ductus arteriosus, and that found in those patients in whom pulmonary hypertension is acquired later in life, as with an atrial septal defect or mitral stenosis on a rheumatic basis.

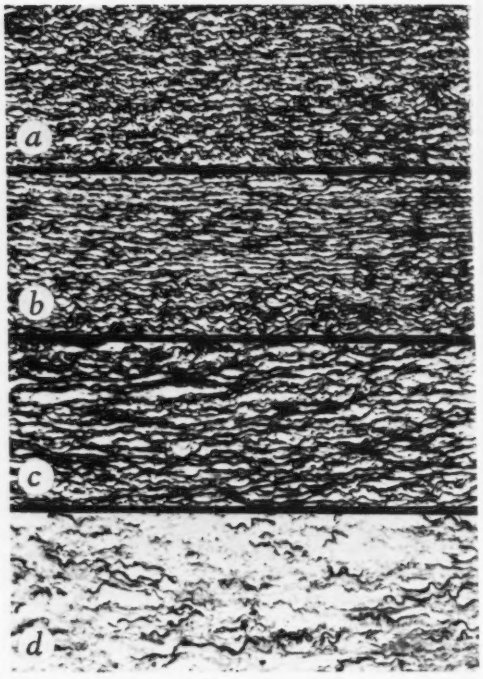

Figure 1

Photomicrographs of transverse sections of control pulmonary trunk and aorta (elastic-tissue stain; × 100). a. *Pulmonary trunk from a 46-hour-old boy, showing the normal aorta-like fetal configuration of the media.* b. *Ascending aorta from a 46-hour-old boy, showing the normal aortic configuration of the media.* c. *Ascending aorta in a 53-year-old man, showing the normal aortic configuration of the media.* d. *Pulmonary trunk in a 53-year-old man, showing the normal adult pulmonary configuration of the media.*

The configuration of the elastic tissue does not appear to be determined by the magnitude of the pulmonary blood flow or by the absolute levels of either the systolic or pulse pressure in the pulmonary artery. We[3] found previously, for example, that the configuration of elastic tissue was of the fetal, aorta-like type in a 1½-year-old child who had a ventricular septal defect and a pulmonary blood flow of 7.4 L./min./M.^{2}, but that it was of the adult

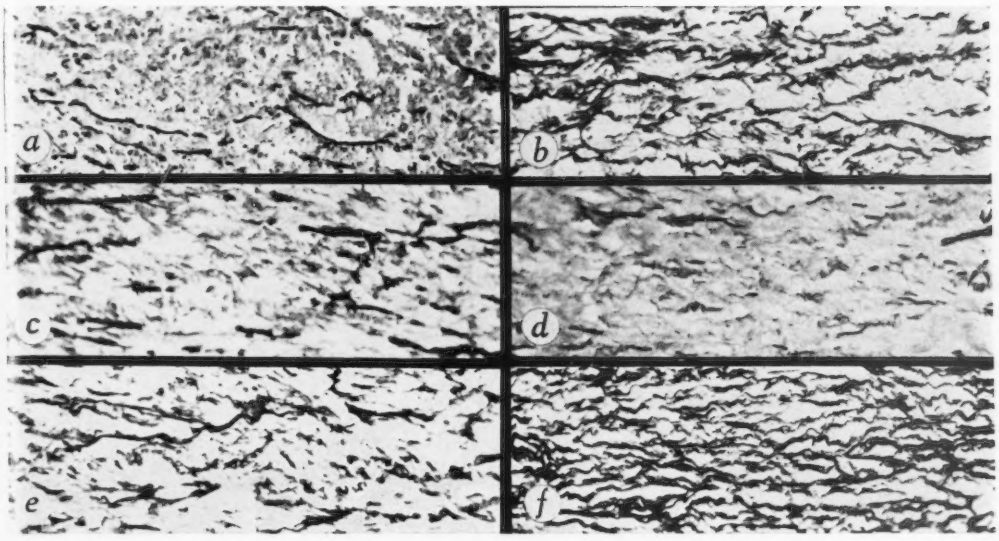

Figure 2

Photomicrographs of pulmonary trunk in cases 1-6 (elastic-tissue stain; × 150). a-e. Appearance in cases 1-5, respectively, showing adult pulmonary configuration of the media in each. f. (Case 6). Note the aortic type of medial configuration in this case. (The authors acknowledge with thanks the receipt of material in case 2 from Dr. Morgan Berthrong, Glockner-Penrose Hospital, Colorado Springs, Colorado.)

pulmonary type in a 27-year-old woman with atrial septal defect and a similar pulmonary blood flow of 6.7 L./min./M.^{2}; both these patients had pulmonary hypertension. In the present series also, one patient (case 3) had an adult pulmonary configuration of elastic tissue with a pulmonary blood flow of 1.9 L./min./M.^{2}, whereas in another patient (case 6) who had a virtually identical flow of 2.1 L./min./M.^{2}, the pattern was much more like that found in the normal fetus. Similarly, the absolute level of pulse pressure in the pulmonary trunk apparently does not determine the configuration of the elastic tissue in the wall; thus, in case 3, a pulse pressure of 42 mm. Hg in this artery was associated with an adult pulmonary configuration, whereas in the aorta in the same case, a virtually identical pulse pressure of 36 mm. Hg was associated with a typical aortic pattern of elastic tissue.

On the basis of data of this type, we think it likely that the configuration of elastic tissue in the pulmonary trunk is an expression of the time of onset of the pulmonary hypertension. When the hypertension is present from birth, as in large ventricular septal defects, the fetal configuration, closely resembling that of the adult aorta, is retained; however, when the increase of pressure occurs after the normal transition of the elastic tissue into the adult form, as in mitral stenosis caused by rheumatic fever, the pulmonary trunk thickens but the aorta-like configuration is not regained.

With the acceptance of this histologic criterion as an indicator of the time of onset of pulmonary hypertension, the presence of the adult configuration in our 5 female patients ranging in age from 12 to 54 years (fig. 2*a-e*) may be interpreted as indicating that the pulmonary hypertension was acquired in these cases. The finding of a configuration of elastic tissue more closely resembling that of the fetus in case 6 (fig. 2*f*) suggests that pulmonary hypertension was present from birth in this instance, thereby supporting the view

of Wade and Ball[4] that "primary pulmonary hypertension" may be a heterogeneous group of diseases.

Summario in Interlingua

Esseva studiate le configuration del histos elastic del trunco pulmonar in 6 casos de idiopathic hypertension pulmonar. Le etates del patientes variava inter 12 e 54 annos. Le configuration esseva illo del typo pulmonar adulte in le 5 patientes feminin sed resimulava plus intimemente le typo fetal aortoide in le unic patiente mascule. Iste datos es interpretate como indication que idiopathic hypertension pulmonar es acquirite in le majoritate del casos sed que illo pote esser presente a partir del nascentia in un minoritate de casos.

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Amedeo Avogadro

Two thousand years ago Lucretius in Rome expounded the doctrine of atoms. He expressed in immortal language the speculations of the Greek philosophers, and he described with the vividness of a great poet the movements, the unions and separations of the tiny corpuscles of which he conceived all things to be composed. The atoms had many qualities which modern science assumes even today. Vigorous motion under the appearance of rest, penetration of heat and cold depending on this movement, hooks for attachment to others, and even an unpredictable "clinamen" or swerve, which is a sort of fantastic anticipation of the uncertainty principle of quantum mechanics.

This was magnificent and represented a wonderful intuitive insight into the working of nature, but it was not science. There was no link with quantitative experimentation, the construction of which connection was lacking until modern times. Then, one might say suddenly, the science of chemistry was created by the vision of a few great men, among whom was Amedeo Avogadro (1776-1856).

The recognition by Avogadro of the distinction between atoms and molecules was the key which opened the treasury of structural chemistry; a treasury whose riches are not yet exhausted. The establishment of the true doctrine about the nature of the particles of the elementary gases rendered possible the development of the kinetic theory and the understanding of the energy relationships of these particles.

On this basis was founded the study not only of the structure of substances but of the functional relationships that govern chemical change: chemical kinetics. A true doctrine of molecules was the necessary precursor of what may truly be called both the anatomy and the physiology of chemical compounds.

There is irony in the fact that the importance of Avogadro's work was not understood for 40 years. This has a course happened to other men of science, and it should perhaps remind us that the advance of knowledge is in some measure an impersonal thing. However this may be, there is no doubt that one of the best ways of honoring the memory of the great scientists of the past is by considering the progress that has been made on the basis of their original labors.—Cyril N. Hinshelwood, *Science* **124**: 708, 1956.

The Vectorcardiogram and Electrocardiogram in Persistent Common Atrioventricular Canal

By JONAS BEREGOVICH, M.D., SELVYN BLEIFER, M.D., EPHRAIM DONOSO, M.D., AND ARTHUR GRISHMAN, M.D.

The electrocardiogram and vectorcardiogram are of great aid in differentiating atrial septal defect of the secundum type from the ostium-primum type. In the latter condition there is left axis deviation in the scalar electrocardiogram and superior orientation of the QRS vector in the sagittal and frontal planes. There are relatively few congenital lesions that lead to the same degree of axis deviation and superior orientation of the QRS vector.

THE importance of accurate anatomic differentiation preoperatively between the ostium primum and secundum types of atrial septal defects cannot be overemphasized. The ostium secundum type is technically the most simple intracardiac communication to repair and is amenable to several operative technics such as the atrial well, hypothermia, and pump oxygenator bypass. The persistent common atrioventricular canal is more difficult to repair and the surgical procedure requires direct vision for correction of all the malformations.[1, 2]

In the last few years, the pathologic studies of Wakai and Edwards,[3] and Campbell and Missen,[4] have clarified the anatomic features of this malformation in which, besides the low atrial septal defect, there may be a cleft in either or both atrioventricular valves, as well as a defect in the membranous portion of the ventricular septum. Another common finding is the occurrence of combined ventricular hypertrophy.

The differentiation of the 2 types of defects on clinical and hemodynamic grounds alone is often difficult. Several authors[5-8] have described electrocardiographic findings that have proved to be reliable for this differentiation. Toscano-Barbosa et al.[5] also called attention to a rather characteristic vectorcardiographic pattern, which they described only for the frontal plane.

The purpose of this communication is to present our vectorcardiographic and electrocardiographic experience in a group of cases of persistent common atrioventricular canal.

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Material and Method

The material is comprised of 18 patients studied at The Mount Sinai Hospital from 1955 to 1959. Selection was made on the basis of a complete history, physical examination, chest x-rays, electrocardiograms, and vectorcardiograms. Right heart catheterization was performed in every instance. In 2 patients selective angiocardiography was performed. The dye was injected into the left ventricle and regurgitation into the left or right atrium or right ventricle was demonstrated. In another 7 patients, anatomic confirmation of a persistent common atrioventricular canal was subsequently obtained at operation.

There were 10 female and 8 male subjects in our series, with ages ranging from 2½ to 42 years.

Routine 12-lead electrocardiograms were obtained with the direct writing Technicon or Sanborn Viso-Cardiette. Simultaneous leads and double paper speed (50 mm./sec.) were used in several instances.

The vectorcardiograms were obtained with the Sanborn Vector System and Viso-scope. The cube method of electrode placement was used.[9] The horizontal, sagittal, and frontal planes of the vectorcardiogram were analyzed for spatial orientation, configuration, and direction of inscription of the QRS and T loops.

When applicable, the criteria used for the electrocardiographic diagnosis of right ventricular hypertrophy were those of Sokolow and Lyon.[10] Goodwin,[11] Milnor,[12] and Barker and Valencia.[13] For left ventricular hypertrophy those of Sokolow and Lyon[14] or Pagnoni and Goodwin[15] were used. Combined ventricular hypertrophy was considered to be present if the criteria of Beregovich et al. were satisfied.[16]

The vectorcardiographic diagnosis of right, left,

Table 1

Electrocardiographic and Vectorcardiographic Observations in Eighteen Cases of Common Atrioventricular Canal

Case	Sex	Age yrs.	RV pres. mm. Hg	PR sec.	QRS sec.	E. Ax.	V_1 pat.	ECG diagnosis	Horizontal Plane Orient.	Rot.	Sagittal Plane Orient.	Rot.	Frontal Plane Orient.	Rot.	Cond. delay
1. R. L.	F	8	80/11	0.14	0.09	—45	rR′	RVH. LVH.	Anterior	c	Superior anterior	cc	Superior left	cc	
2. S. J.	F	7	Marked RV hyp	0.21	0.10	—75	rsR′	RVH. LVH. RAE. LAE?	Anterior right	8	Superior anterior	c	Superior	cc	+
3. L. S.*	F	5	63/5	0.21	0.08	—90	rsR′	RVH. LVH. RAE.	Anterior right	c	Superior anterior	8	Superior left	cc	
4. C. J.*	F	7	33/1	0.17	0.09	—60	rsR′	RVH. LVH. RAE.	Anterior right	c	Superior anterior	c	Superior	cc	
5. B. L.*	M	8	39/0	0.20	0.10	—60	rSR′	RVH. LVH. RAE.	Anterior	c	Superior anterior	c	Superior left	cc	+
6. B. R.	F	42	41/8	0.22	0.10	—75	Rs	RVH. LVH. LAE.	Anterior	c	Superior anterior	c	Superior left	cc	
7. B. R.@*	M	7	38/8	0.24	0.08	—60	rsR′	RVH. LVH. RAE. LAE?	Anterior right	c	Superior anterior	8	Superior	cc	
8. S. B.	F	35	83/0	0.22	0.15	—60	rsR′	LVH. RAE. LAE.	Anterior	c	Superior anterior	cc	Superior	cc	+
9. O. I.@	M	32	56/4	0.26	0.10	—80	rsR′	RVH? LVH. RAE?	Anterior	8	Superior anterior	8	Superior	cc	
10. P. L.	F	2½	80/0	0.17	0.07	Conc. S	rR′	RVH. RAE.	Anterior right	c	Superior anterior	c	Superior right	cc	
11. S. S.	M	4	80/0	0.15	0.07	Conc. S	RR′	RVH.	Anterior	8	Superior anterior	cc	Superior right	cc	
12. R. V.	M	5	45/3	0.16	0.08	Conc. S	rsR′	RVH. RAE.	Anterior	8	Superior anterior	cc	Superior right	8	
13. R. A.*	M	4	Moder. RV hyp	0.24	0.08	Conc. S	qR	RVH.	Anterior right	c	Superior anterior	c	Superior	cc	
14. T. B.	F	4	33/	0.14	0.10	—60	rsR′	LVH?	Termin. segm. right-ant.	cc	Superior anterior	c	Superior	cc	+
15. T. G.	M	14	35/4	0.25	0.09	—75	rSr′	LVH. RAE? LAE?	Termin. segm. right-ant.	cc	Superior anterior	cc	Superior left	cc	+
16. B. J.	F	14	38/8	0.24	0.09	—60	rsR′	RVH. LVH. RAE. LAE?	Termin. segm. right-ant.	cc	Superior	cc	Superior left	cc	+
17. V. L.*	M	8	30/0	0.18	0.08	—60	qs	LVH. RAE.	Termin. segm. right-post.	cc	Superior posterior	cc	Superior left	cc	+
18. K. A.*	F	16	47/5	0.21	0.08	—30	rS	LVH. LAE.	Left posterior		Superior posterior	c	Superior left	cc	

(Explanation of abbreviations on bottom of opposite page)

and combined ventricular hypertrophy, based on studies made in this laboratory,[9, 16, 17] could not be satisfactorily applied in these cases.

Results

Vectorcardiograms (Table 1)

A constant finding was superior orientation of the QRS loop in the frontal and sagittal planes. A small initial segment may be directed inferiorly, but by far the largest portion of the QRS loop was superiorly oriented.

In the frontal plane, the QRS loop was directly superior or slightly displaced to the left in 15 cases (fig. 1), and somewhat displaced to the right in 3 cases (fig. 2). The sense of rotation was counterclockwise in all but 1 tracing, in which the loop was a figure-of-eight (case 12).

In the sagittal plane the QRS loop was superiorly and anteriorly oriented in 16 cases, superior and somewhat posterior in 2. The sense of rotation was variable.

In the horizontal plane the QRS loop showed no consistent pattern. There were loops similar to those described for right ventricular hypertrophy in 13 cases (nos. 1 to 13), the orientation being anterior, to the right, and clockwise (figs. 1 and 2). When the loop had a figure-of-eight configuration, the terminal limb was always clockwise (fig. 3).

In 3 other cases (nos. 14–16) the QRS loop in the horizontal plane was similar to that described for right bundle-branch block, with the initial portion of the loop normally oriented, but with a terminal segment anterior, to the right, and slowly inscribed. The terminal limb of this segment was clockwise in rotation (fig. 4).

In 1 case (no. 18) (fig. 5) the QRS loop in the horizontal plane was within normal limits, and the remaining case (no. 17) showed an unusual loop that could not be classified.

The T loop, in general, was discordant or at an angular deviation from the main area of the QRS loop.

Electrocardiograms (Table 1)

There was a sinus rhythm in all 18 cases; however, in 11 electrocardiograms the P-R intervals were prolonged for the heart rate and age.[18] Left axis deviation was observed in 14 cases, and this group coincides with those whose frontal plane vectorcardiogram was superior or slightly displaced to the left (fig. 3). In the 4 remaining cases (nos. 10–13) a concordant S pattern was found in the standard leads. This group corresponded to those with a superior and rightward displaced QRS loop in the frontal plane (fig. 2).

In 11 electrocardiograms there was a RSR′ pattern in V_1 (figs. 3 and 4). However, rR′, Rs, rS, qR, or QS patterns in V_1 were also observed (figs. 1 to 5). An RSR′ pattern in the right precordial leads was not considered sufficient evidence for a diagnosis of right bundle-branch block in this group of patients because the vectorcardiogram does not always show a conduction delay.

On the basis of electrocardiographic criteria, a diagnosis of combined ventricular hypertrophy was made in 9 cases (nos. 1–7, 9, 16) (fig. 3). In the 4 patients with a concordant S pattern (nos. 10–13), right ventricular hypertrophy was diagnosed (fig. 2); and in the 5 remaining cases (nos. 8, 14, 15, 17, 18), the diagnosis was left ventricular hypertrophy (fig. 5).

Intracardiac Pressures

Moderate to marked elevation of right ventricular and pulmonary artery pressures was a frequent finding. Right ventricular pressures of 45 mm. Hg or more were observed in 10 cases.

RVH: Right ventricular hypertrophy.
LVH: Left ventricular hypertrophy.
RAE: Right atrial enlargement.
LAE: Left atrial enlargement.
?: Questionable diagnosis.
Concd. S.: Concordant S pattern.
Rot: Rotation.
c: Clockwise rotation.
cc: Counterclockwise rotation.
8: Figure-of-eight rotation.
Cond. delay +: Presence of conduction delay.
RV hyp: Right ventricular hypertension (no exact figures available)
@: Selective angiocardiography.
*: Surgical correction.

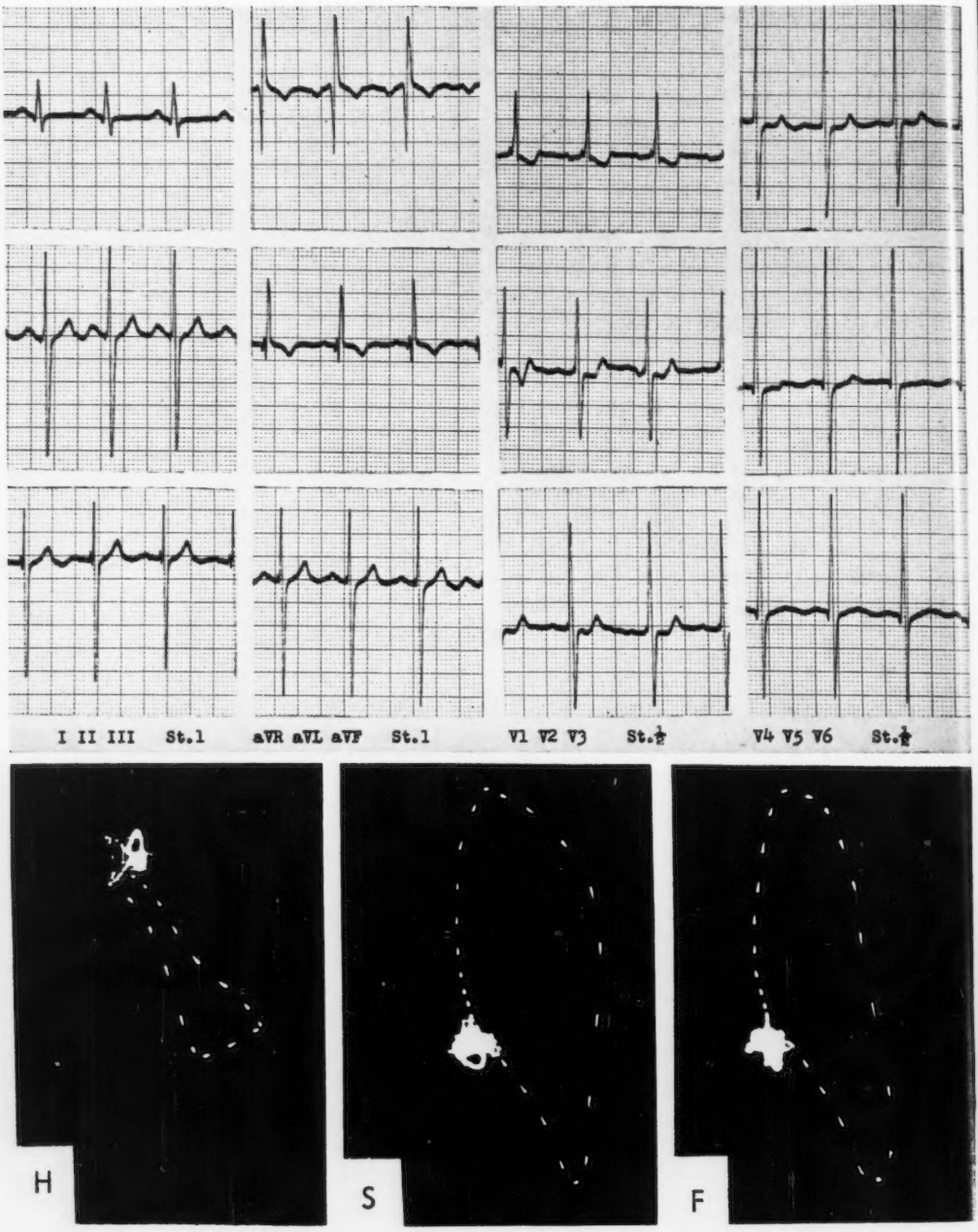


Figure 1

R.L., case 1. The QRS loop is superiorly oriented in the sagittal and frontal planes. Note leftward displacement of the QRS loop in the frontal plane and counterclockwise rotation; in the horizontal plane, anterior displacement and clockwise rotation of the QRS loop. Left axis deviation and an rR' pattern in V_1 are shown in the electrocardiogram.

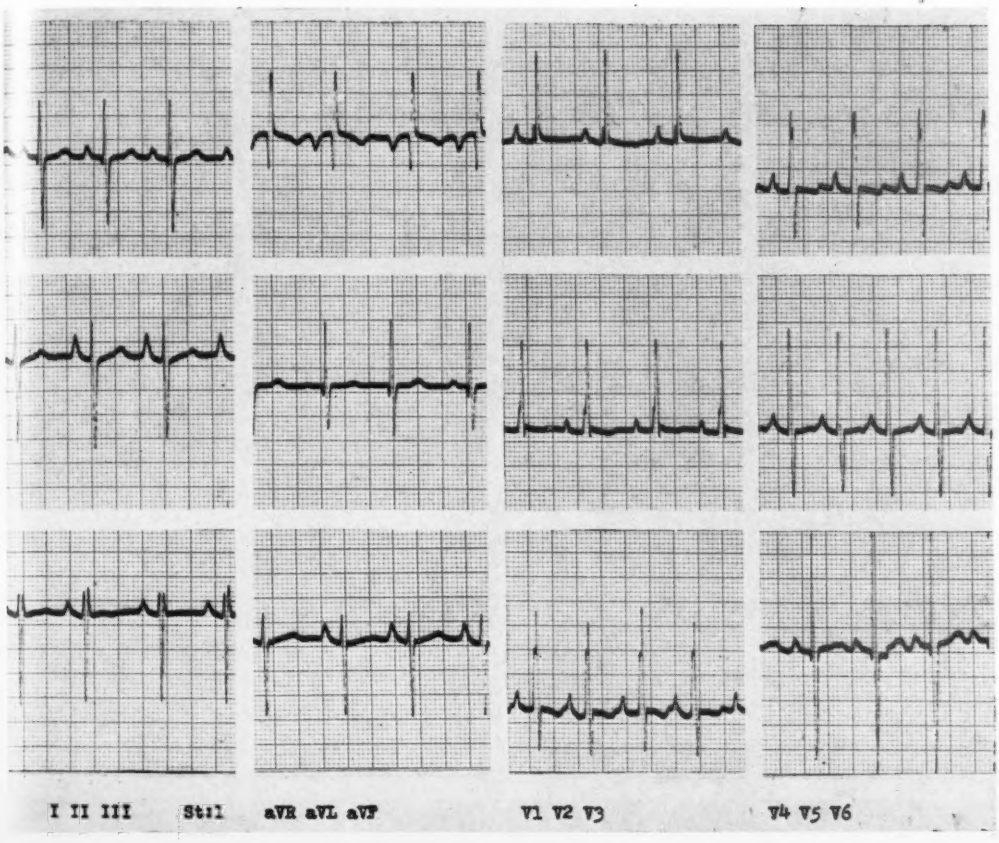


Figure 2

P.L., case 10. There is superior orientation of the QRS loop, which is displaced to the right in the frontal plane. There is a concordant S pattern in the standard leads of the electrocardiogram. An rR' pattern is present in V_1.

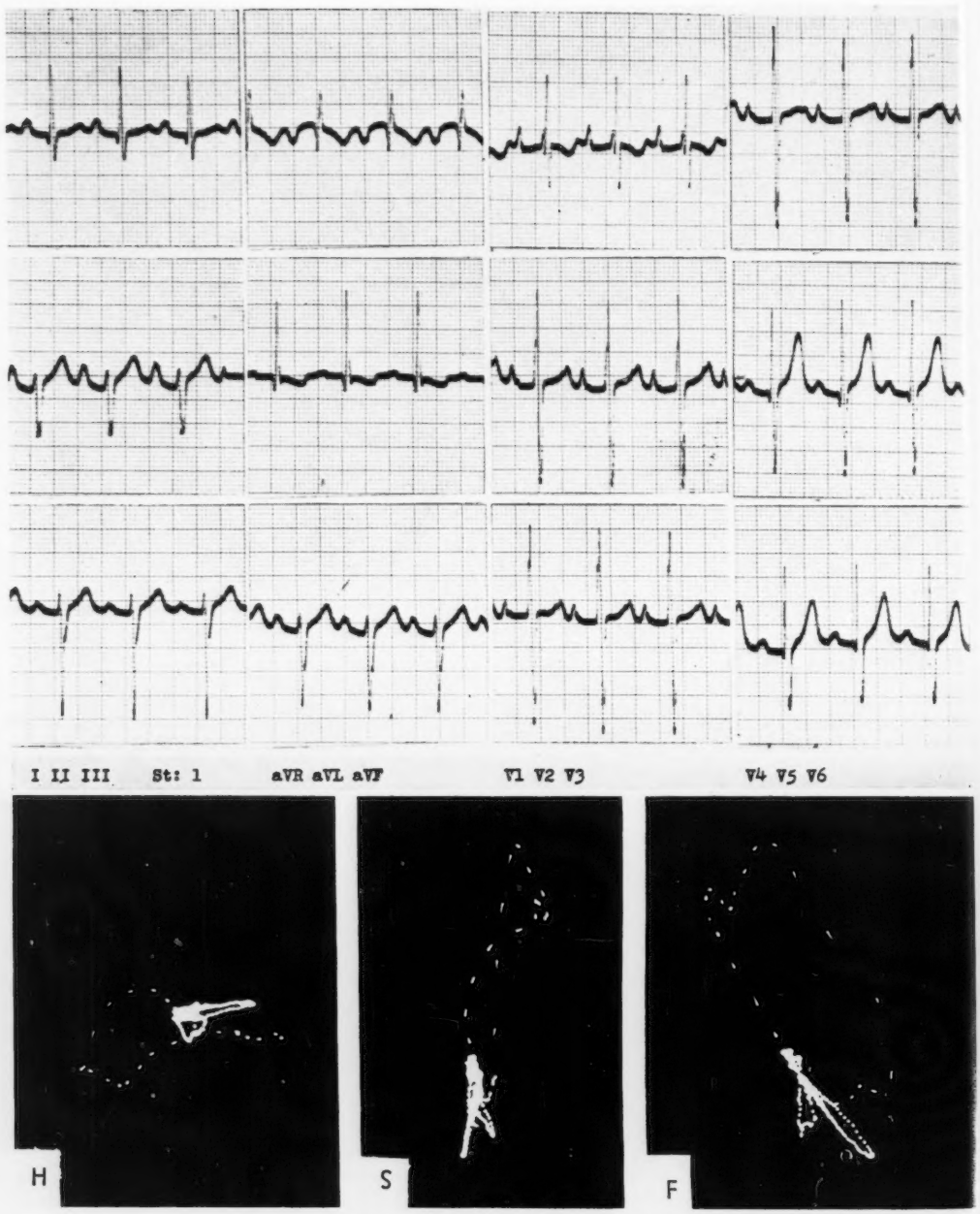
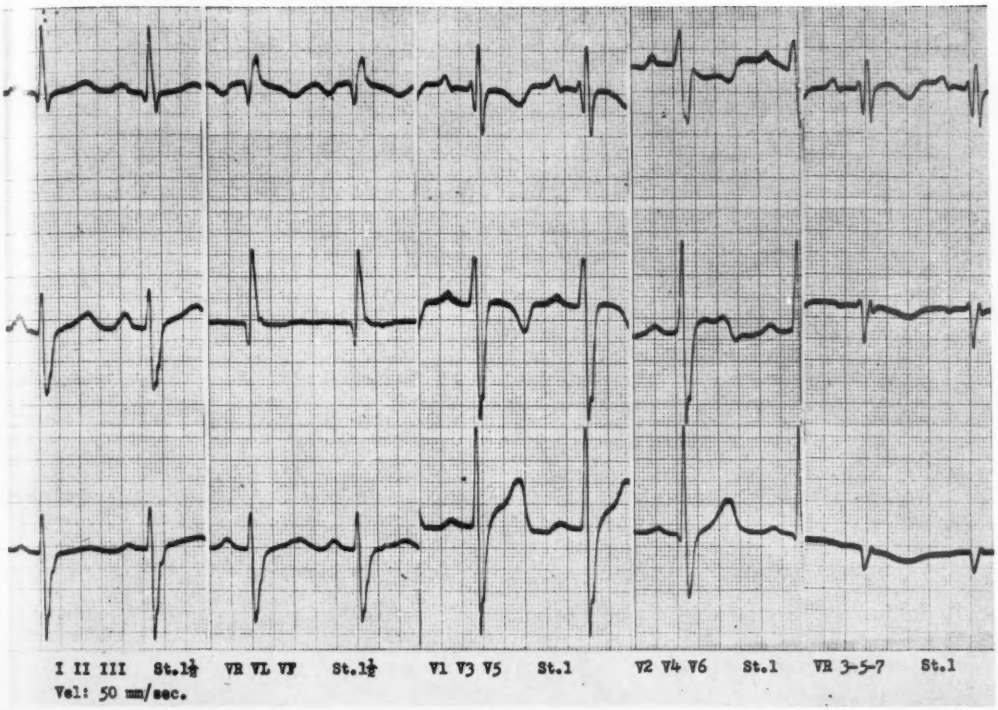


Figure 3

B.R., case 7. (The diagnosis was confirmed by selective angiocardiography and surgical correction.) There is superior orientation of the QRS loop in the sagittal and frontal planes with counterclockwise rotation in the frontal plane. The horizontal plane shows a figure-of-eight pattern. Electrocardiogram shows first-degree atrioventricular block, left axis deviation, and RSR' pattern in V_1.



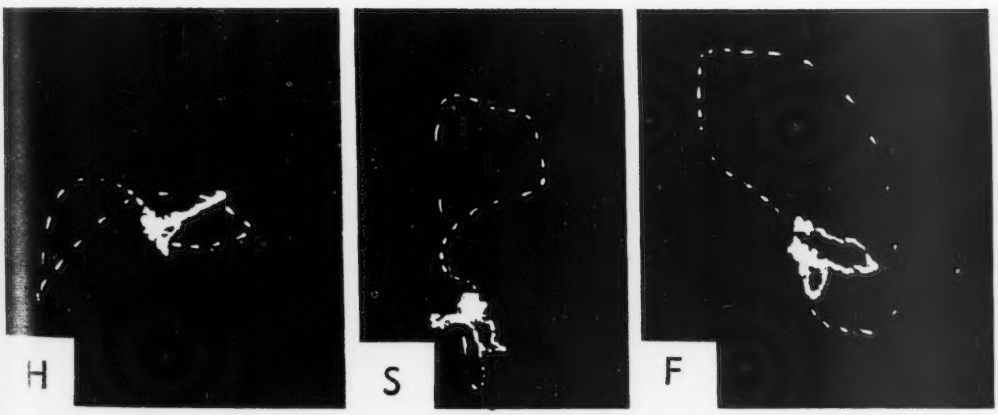


Figure 4

T.B., case 14. There is superior orientation of the QRS loop in the frontal and sagittal planes. The terminal limb is slightly delayed. In the horizontal plane the terminal segment is anterior and to the right, resembling the configuration of right bundle-branch block. Electrocardiogram shows left axis deviation and an rSR' pattern in V_1.

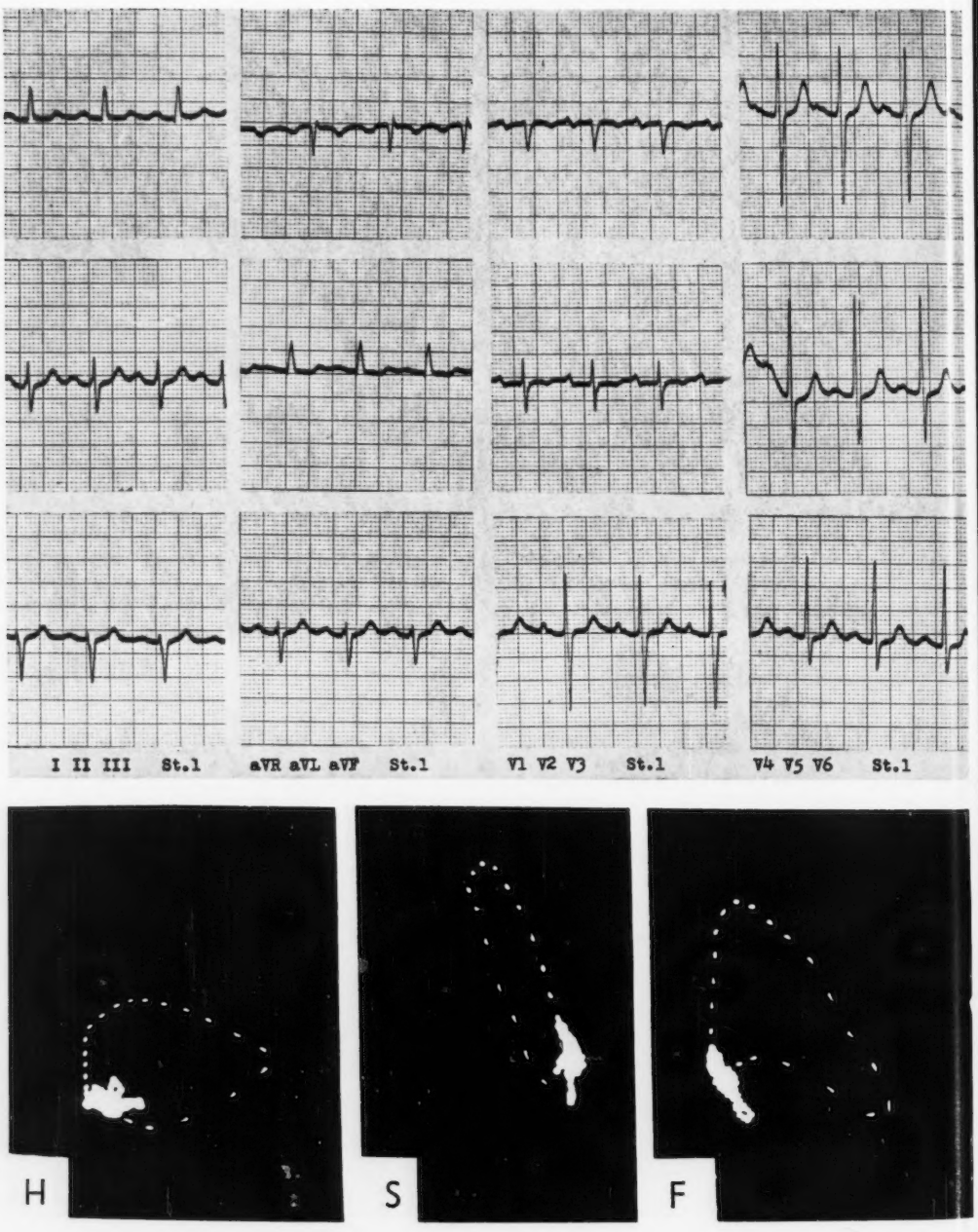


Figure 5

K.A., case 18. (Diagnosis proved at operation.) There is superior orientation of the QRS loop in the sagittal and frontal planes. The horizontal plane QRS loop, however, is normal. Electrocardiogram shows left axis deviation, first-degree atrioventricular block, and an rS pattern in V_1.

No correlation existed, however, between right-sided pressures obtained at catheterization and the vectorcardiographic or electrocardiographic patterns.

Discussion

Several clinical and hemodynamic points are suggestive but not diagnostic of a persistent common atrioventricular canal. Marked cardiomegaly, an apical thrill, murmurs of mitral or tricuspid regurgitation, cyanosis, or evidence of pulmonary hypertension leads one to suspect such a possibility when the remainder of the clinical picture is that of an atrial septal defect.[6, 19]

From catheterization studies it has been learned[6, 20] that the following findings also favor the presence of a persistent common atrioventricular canal type of defect: (1) a low position of the catheter when the defect is crossed; (2) entrance of the catheter from the right atrium directly into the left ventricle; (3) left-to-right shunt at the right atrial level and occasionally an additional oxygen step-up in the right ventricle; (4) a high incidence of marked right ventricular and pulmonary artery hypertension; (5) left ventriculography demonstrating regurgitation of dye from the left ventricle to the right atrium.[21] These findings are not pathognomonic, and the clinical diagnosis remains a difficult one.

The electrocardiogram and vectorcardiogram have proved to be the greatest single aid to the clinician.

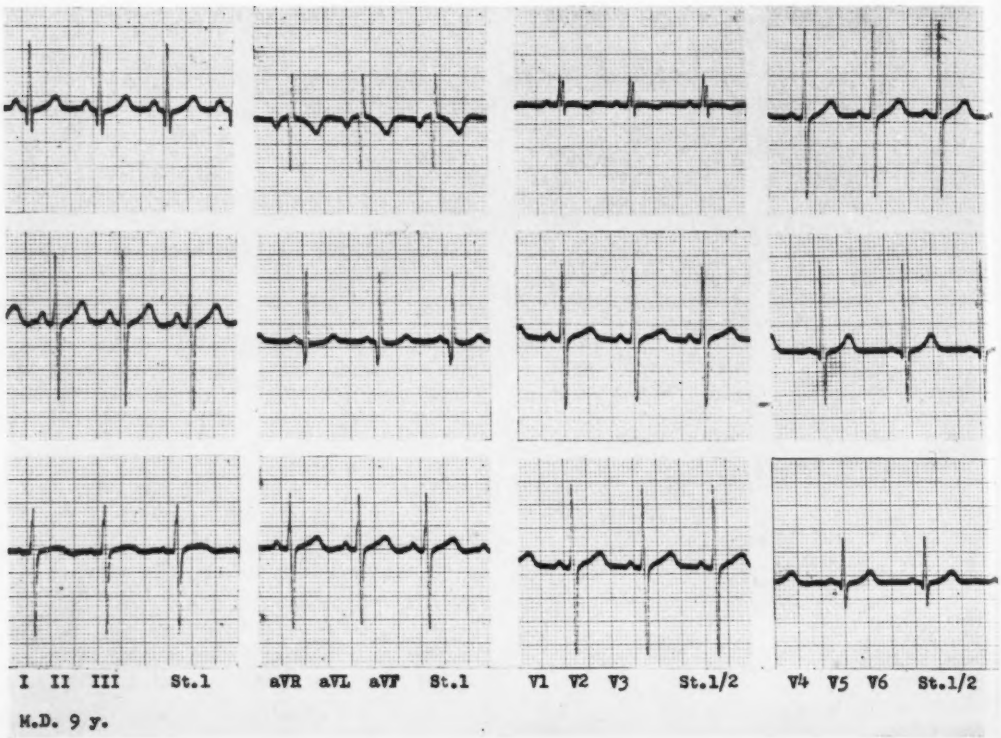
The diagnostic value of the electrocardiogram was generally confirmed in our series, and in many cases the electrocardiograms was similar to those described previously.[5, 7] Normal sinus rhythm, frequent occurrence of first-degree atrioventricular block, left axis deviation or occasionally a concordant S pattern in the standard leads, and an RSR′ pattern in V_1 were the most outstanding electrocardiographic findings. These features are by no means constant, however. A variety of other electrocardiographic patterns was observed in V_1; and with application of strict criteria, a diagnosis of either combined, right, or left ventricular hypertrophy could be made in all cases.

Similar electrocardiograms, with left axis deviation, have been observed in other congenital malformations such as ventricular septal defects[16] (fig. 6) and tricuspid atresia. The frontal plane vectorcardiogram in these cases is different, however; it shows a leftward displacement of the QRS loop, but its major portion is not superiorly oriented but is rather inferiorily or horizontally displaced.

The vectorcardiogram shows very constant characteristics in persistent common atrioventricular canal. The outstanding features are superior orientation of the QRS loop in the frontal and sagittal planes, and counterclockwise rotation of the QRS loop in the frontal plane. A small difference in the displacement of the QRS loop in the frontal plane accounted for either a leftward or rightward loop which was insignificant vectorially, but electrocardiographically caused a marked change. When there was leftward displacement of the QRS loop, left axis deviation was observed, and with rightward displacement a concordant S pattern resulted.

The horizontal plane QRS loop configuration, in this particular group, seems to be less valuable as an aid in the diagnosis. Slight differences in displacement of the superiorly oriented electrical forces, account for the variability in the horizontal plane projection, and for different QRS loop patterns.

In some cases a terminal slowing appears of the QRS loop somewhat beyond that seen in normal subjects. Distinct from right bundle-branch block, it remains within the general contour of the QRS loop and does not appear as a separate segment (at least in the frontal and sagittal planes). Since in the cases of persistent common atrioventricular canal the QRS loop is superiorly oriented, its terminal segment likewise has a perpendicular orientation (fig. 4). Very occasionally almost the entire centripetal limb is slowed. There was no consistent relationship to the duration of the QRS complexes, although with pronounced terminal slowing, increased QRS in-



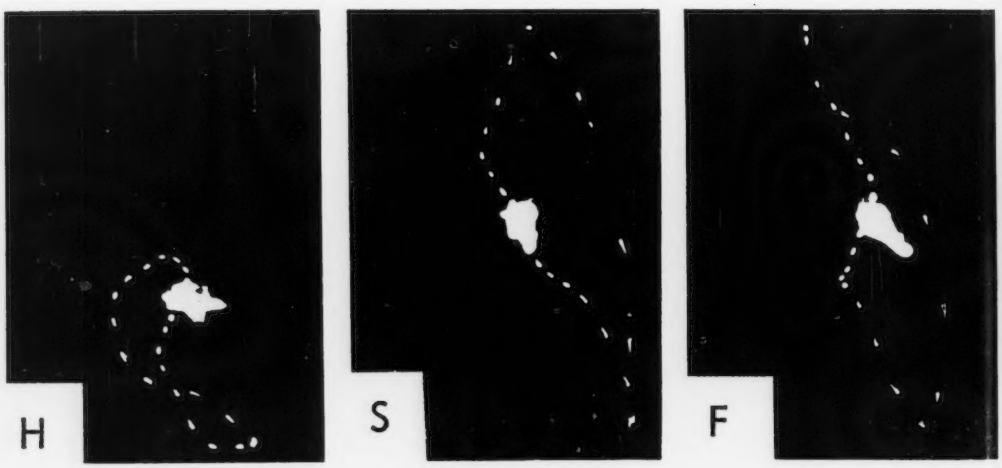


Figure 6

M.D., a 9-year-old girl with a ventricular septal defect. There is leftward displacement of the QRS loop in the frontal plane but a significant portion of the loop is inferior in the sagittal and frontal plane. There is a figure-of-eight loop anteriorly displaced in the horizontal plane. Electrocardiogram shows left axis deviation and an RSR' pattern in V_1.

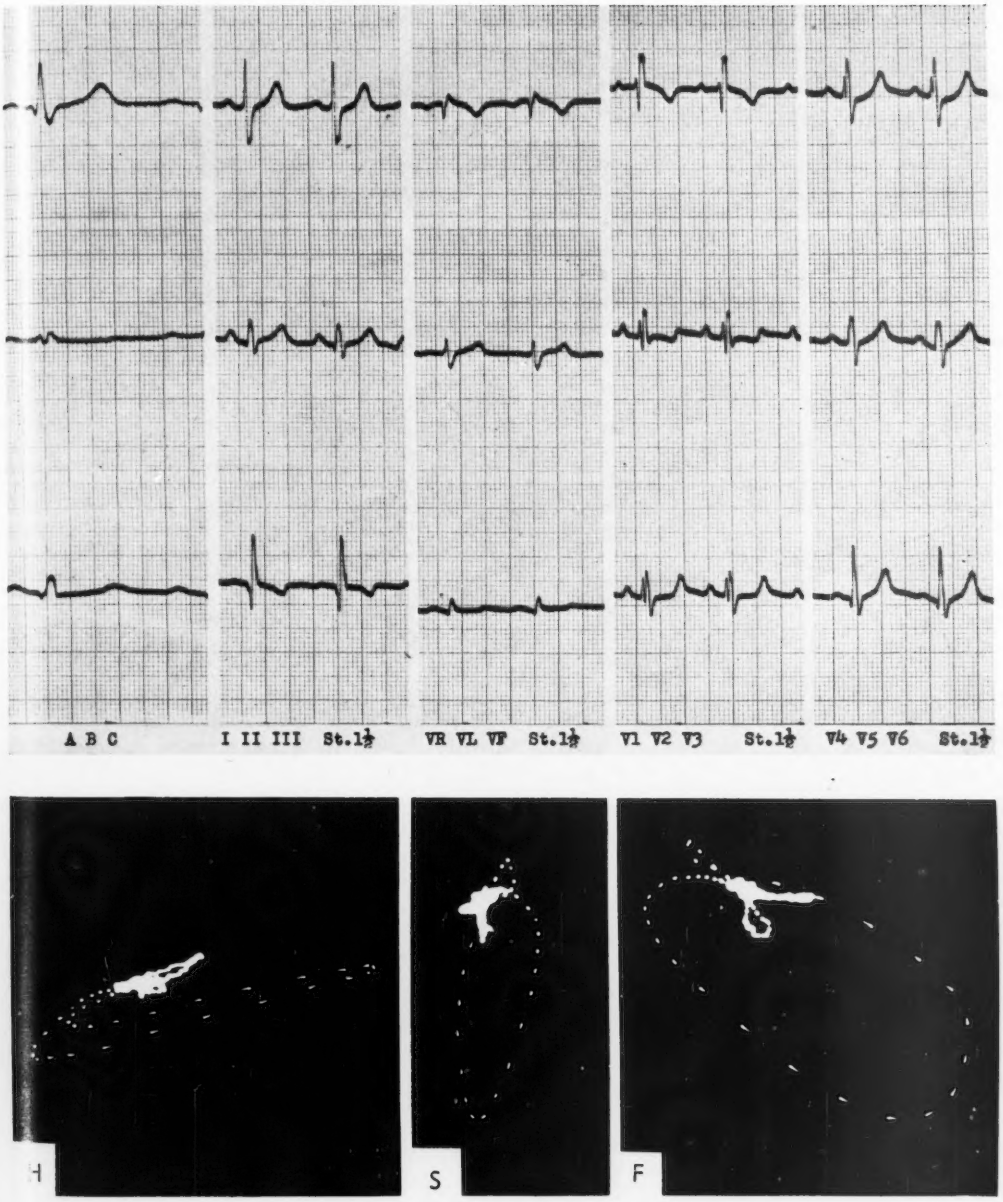


Figure 7

R.E., a 17-year-old patient with an ostium secundum type defect, subsequently confirmed at operation. The vectorcardiogram shows inferior orientation of the QRS loop in the sagittal and frontal planes. The QRS loop is inscribed clockwise in the frontal plane. There is also clockwise rotation and anterior displacement of the QRS loop in the horizontal plane. Electrocardiogram shows right axis deviation and an rSR′ pattern in V_1.

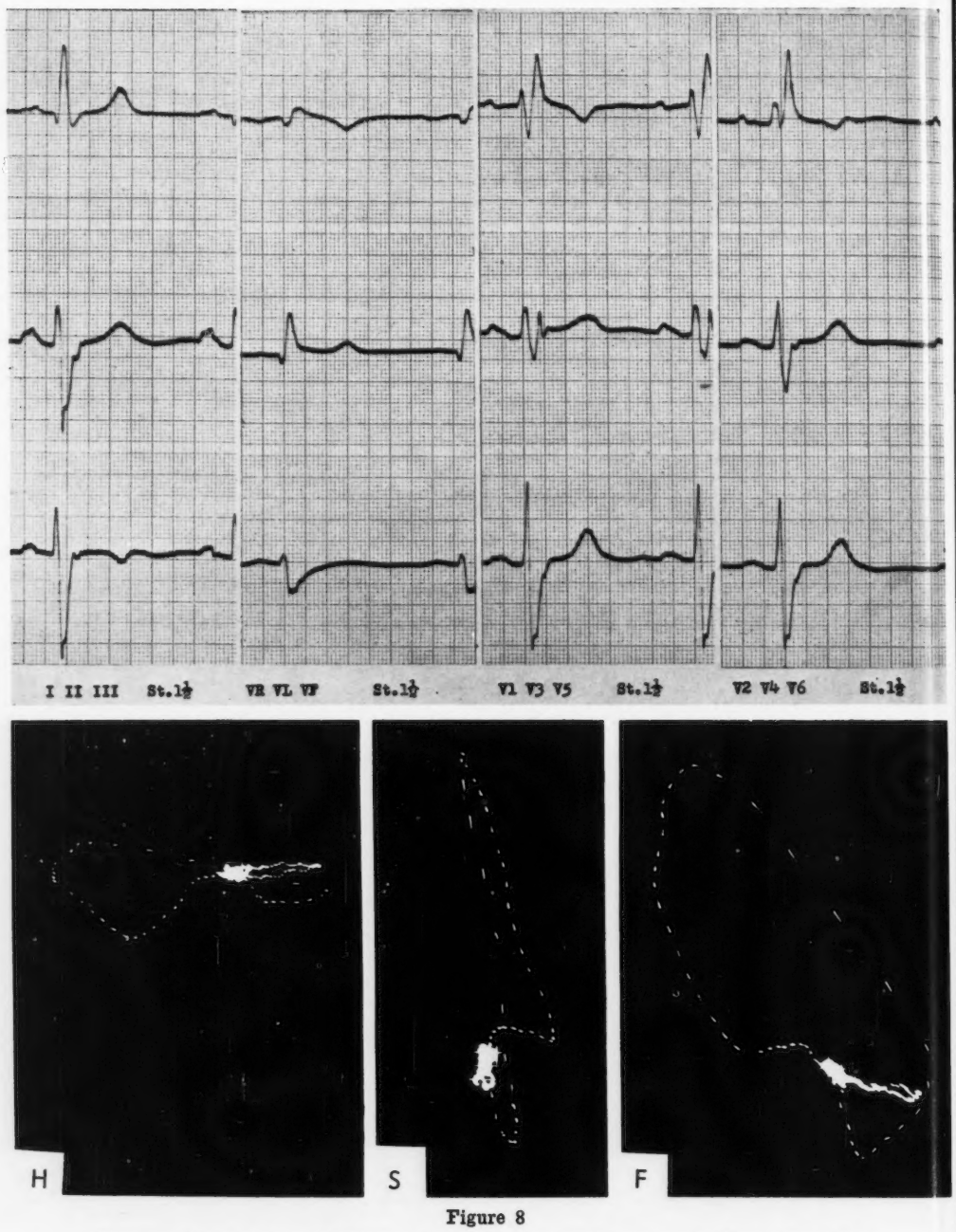


Figure 8

Vectorcardiogram of an elderly patient with coronary atherosclerosis. Note similarity to the patterns illustrated in cases of AV-canal defects. The QRS loop is superiorly oriented. In this case there is terminal conduction delay. Electrocardiogram (double paper speed) shows left axis deviation and an rSR' pattern in V_1.

terminals were more likely to be encountered. The spatial orientation and gradual transition from the main QRS loop, set it apart from right bundle-branch block of the Wilson type, where the terminal, slowed segment is a sharply delineated appendage to the main QRS loop and invariably oriented to the right, anteriorly, and essentially within the horizontal plane.

The significance of the superior orientation of the vectorcardiogram is not known. It is tempting to assume that this is caused by combined ventricular hypertrophy, since pathologically this is a frequent finding. It is not justifiable with our present knowledge, however, to make such a statement. It is just as likely to be due to a difference in the course of ventricular activation, since the defect is so intimately related to the conducting system. For this reason, we have avoided making specific vectorcardiographic diagnosis, and we have preferred merely to describe the morphologic configuration. This may also apply to the use of electrocardiographic criteria for the identification of right, left, or combined ventricular hypertrophy in the electrocardiogram of this group of patients.

The vectorcardiogram is quite different from those observed in the ostium secundum type of defect[22] (fig. 7) and serves as an excellent aid in the differential diagnosis.

In our experience the only instance in which a similar vectorcardiographic pattern is observed occurs in old patients with left ventricular hypertrophy and coronary disease:[23] superior orientation with conduction delay in the second half of the QRS loop is observed (fig. 8). The electrocardiogram might be interpreted as right bundle-branch block with left axis deviation. The differences in age and clinical findings are such that confusion rarely exists. When a vectorcardiographic pattern similar to that described above is observed in a patient with congenital heart disease, one must strongly consider the probability of persistent common atrioventricular canal.

Summary

The vectorcardiogram and electrocardiogram in 18 cases of persistent common atrioventricular canal have been described.

Vectorcardiographically superior orientation of the QRS sÊ loop as seen in the sagittal and frontal planes and counterclockwise rotation of the QRS sÊ loop in the frontal plane were constant findings. In the horizontal plane a variety of different QRS sÊ loop configurations were observed.

Electrocardiographically the most frequent findings were first degree AV block, left axis deviation or concordant S pattern, and RSR′ pattern in V_1, although other configurations were also observed.

The significance of the superior orientation is discussed and the usefulness of the vectorcardiogram in the clinical diagnosis of persistent common atrioventricular canal is pointed out.

Acknowledgment

We wish to express our appreciation to Dr. Alvin J. Gordon, head of the cardiac catheterization team, who so kindly allowed us to use the catheterization data, and to Miss Ruth Jaspan, whose assistance in this study was invaluable.

Summario in Interlingua

Es describite le vecto- e electrocardiogrammas in 18 casos de persistente canal atrioventricular commun.

In le vectocardiogrammas, orientation superior del ansa QRS sÊ (viste le planos sagittal e frontal) e rotation sinistrorse del ansa QRS sÊ in le plano frontal esseva constatationes constante. In le plano horizontal, un varietate de differente configurationes del ansa QRS sÊ esseva observate.

In le electrocardiogrammas, le constatationes le plus frequente esseva bloco atrioventricular del prime grado, deviation axial sinistrorse o concordante patrono S, e patrono RSR′ in V_1, sed altere configurationes esseva etiam observate.

Le signification del orientation superior es discutite. Es signalate le utilitate del vectocardiogramma in le diagnose clinic de persistente canal atrioventricular commun.

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Coronary Embolism Following Repair of a Ventricular Septal Defect

By WILLIAM L. WINTERS, JR., M.D., ELIZABETH V. LAUTSCH, M.D., AND LOUIS A. SOLOFF, M.D.

CORONARY embolism, in contrast to coronary atherosclerosis or thrombosis, is a rare cause of myocardial infarction. Virchow,[1] in 1856, was the first to describe this accident and also to trace its source to bacterial endocarditis. Saphir[2] and Hamman[3] found dislodgment of bacterial vegetations from the aortic or mitral valve to be responsible for the majority of cases. Other causes were thrombic or atherosclerotic material in a coronary artery, thrombi covering atherosclerotic plaques at the root of the aorta, intracardiac mural thrombi, thrombi in pulmonary veins and paradoxical emboli from peripheral veins. To these causes should have been added emboli of neoplastic origin.[4] Later, a unique instance of calcific embolus originating in a nodular calcified aortic valve free of bacterial endocarditis was reported.[5] The introduction of cardiac valvular surgery has made this lesion a not uncommon one.[6]

We report herein another unique cause of coronary embolism, open-heart surgery for repair of a ventricular defect, a cause which may not remain unique for long.

Case Report

C. A., a 17-year-old boy, was first admitted to Temple University Hospital on October 8, 1953, for evaluation of a cardiac murmur present since birth. He had been asymptomatic except for moderate dyspnea, fleeting sharp precordial pain, and cyanosis following strenuous exercise.

Examination revealed retarded physical development, deformity of the anterior chest wall, and findings consistent with a ventricular septal defect. The blood pressure was 100/78. The roentgenogram revealed an enlarged cardiac silhouette and pulmonary artery segment with marked pulsations of its branches. The electrocardiogram was consistent with left ventricular hypertrophy.

Catheterization disclosed pressures of 14/0.5 mm. Hg in the right atrium, 98/17 in the right ventricle, and 98/40 in the pulmonary artery. The oxygen content of the superior vena cava was 10.9 volumes per cent, right atrium 11.1, mid-right ventricle 12.9, high right ventricle 14.6, pulmonary artery 14.4, and radial artery 16.2. The oxygen capacity in the radial artery was 16.9, and its saturation was 96 per cent.

The patient was readmitted on November 13, 1958. He had an episode of syncope, dyspnea, and cyanosis 1 year previously. He complained of recurrent substernal pain lasting 10 to 15 minutes with dyspnea produced by exertion.

Physical examination was unchanged. The roentgenogram showed increased cardiac enlargement. The electrocardiogram was now consistent with right ventricular hypertrophy as well as left. Catheterization disclosed no significant change.

Respiratory functional studies revealed abnormalities considered to be a mixture of a restrictive and obstructive ventilatory problem, consistent with moderate emphysema. All blood studies were normal.

Operation was performed on January 14, 1959. A high ventricular septal defect approximately the size of the aorta was closed with silk. The heart was arrested for 14 minutes. The total time on the pump oxygenator was 25 minutes. The course throughout surgery and for the first 24 hours was uneventful. Then pulmonary congestion and retained secretions increased. Right heart failure developed and the patient died 63 hours after operation.

The postoperative electrocardiogram revealed right bundle-branch block (fig. 1). The subsequent tracings showed abnormal T waves in leads I and II, and on the day of death elevation of the S-T takeoff that was interpreted as due to pericardial reaction. Unfortunately, precordial leads could not be taken because of the surgical dressings.

At autopsy, the heart weighed 670 Gm. The right side of the heart was voluminous; the chambers were dilated. The ventricular wall was hypertrophied to 1.1 cm. in thickness. The left ventricle

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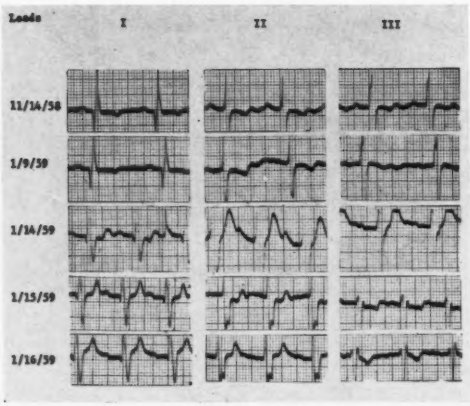

Figure 1

Electrocardiograms after operation.

was dilated and hypertrophied; the wall was 1.6 cm. thick. From this chamber, the high ventricular defect was outlined by a ridge of firm gray-white fibrous tissue. There were minute remnants of adherent thrombus over the defect, directly opposite and a little below the orifice of the left coronary artery. An opening of approximately 0.8 cm. remained at the anterosuperior end of the defect, permitting residual interventricular shunt. The endocardium below the defect was opaque, gray-white, and thickened. In the lower two thirds of the anterior ventricular wall, the inner one third to one half of the myocardium was dull and pale, with yellow, gray, and red mottling. The area extended to the apex and included the anterior two thirds of the interventricular system. The gross appearance was that of a recent subendocardial infarct supplied by the anterior descending branch of the left coronary artery (fig. 2).

The coronary arteries were free of atherosclerosis. However, in the anterior descending branch, 2.5 cm. from its orifice, thrombus material was found occluding the artery for a distance of 3 cm. Beyond was propagated clot. The lungs were congested.

Microscopic sections of the anterior left ventricular wall exhibited extensive subendocardial necrosis. The inner one third of the myocardium was reduced to clumps of deeply eosinophilic material, representing necrotic myocardial fibers. There was unusual edema of the interstitial tissue with infiltration of numerous red blood cells and disintegrating neutrophils. The histologic appearance was that of an infarct, 48 or more hours old (fig. 3). Adherent to the endothelium of the anterior descending branch of the left coronary artery was a minute remnant of thrombus material. The pulmonary arteries showed lipid-rich atherosclerosis and reduction of their lumina.

Figure 2

Left ventricular chamber showing subendocardial infarction and repaired septal defect.

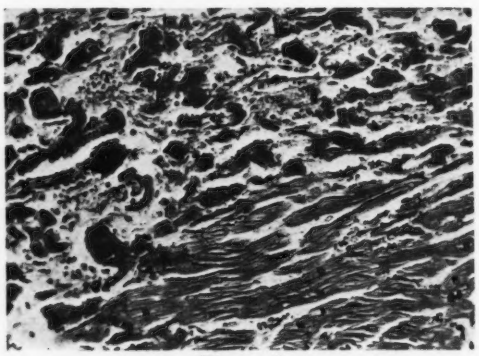

Figure 3

Photomicrograph of left ventricle showing infarction. × 243.

Discussion

The finding at necropsy of an embolus in an anterior descending coronary artery with infarction of the subendocardial region of the anterior left ventricular wall was a complete

surprise to us. From the anatomic relation of the orifice of this vessel and that of the defect and its overlying thrombus, it would appear that coronary emboli could arise at least as frequently from this site as from other regions within the cardiac chambers or from fracture of the aortic or mitral valves. Because the re-institution of anticoagulant therapy (in the absence of contraindications) may be beneficial, it is important to attempt to diagnose this complication at its onset.

It is unlikely that clinical symptoms or signs will be definitive because pain, pulmonary congestion, pulmonary edema, shock, and arrhythmias are common to many complications. The electrocardiogram is the most likely aid in establishing a diagnosis.

Abnormal Q waves would be most definitive, indicating infarction due either to a major coronary embolism or to inadvertent injury to a coronary artery. A current of injury however is a common finding after cardiac surgery due to traumatic pericarditis. Pericarditis was present in our case. This finding alone is therefore of no value in establishing a diagnosis of coronary embolism after cardiac surgery.

On the other hand, we have not encountered the peculiar T-wave changes present in this case in any other postoperative pericarditis. We attributed these T-wave changes to nonspecific myocardial abnormality. Perhaps a detailed study of daily electrocardiograms after open-heart surgery will define the usual changes and unmask patterns characteristic of specific complications.

Summary

A unique cause of coronary embolism is described: open-heart surgery for correction of a ventricular septal defect.

Summario in Interlingua

Es describite un causa unic de embolismo coronari: chirurgia a corde aperte pro corriger un defecto ventriculo-septal.

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Peltzer, F., and Piroth, M.: Clinical and Pathologic Findings in Idiopathic Aneurysm of the Sinus Valsalvae. Ztschr. Kreislaufforsch. 48: 475 (May), 1959.

A 38-year-old man suddenly developed signs of heart failure with a left-to-right shunt and a diamond-shaped systolic murmur with a decrescendo diastolic murmur. The electrocardiogram showed wide diphasic P waves in leads V_1-V_4 and right bundle-branch block with diphasic T in V_5. Autopsy disclosed an aneurysm about 5 cm. long originating immediately above the posterior aortic valve with rupture into the right ventricle.

LEPESCHKIN

Mitral Stenosis in an Atypical Case of Gargoylism:

A Case Report with Pathologic and Histochemical Studies of the Cardiac Tissues

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Severe alterations of cardiac tissue occur in association with complete and incomplete forms of gargoylism. It is the purpose of this paper to record the clinical, pathologic, and histochemical findings in the cardiovascular system of a child with an atypical form of gargoylism and mitral stenosis.

IN 1948, Lindsay emphasized the frequency of cardiac involvement in gargoylism and reported the first case with mitral stenosis at autopsy.[1] Subsequently, the cardiac alterations in typical as well as atypical or incomplete forms of this disorder have been reported.[2-4]

In 1952 Brante demonstrated that the basic abnormality in gargoylism is related to the deposition of acid mucopolysaccharide substances in various tissues. This observation has been substantiated by a number of chemical and histochemical studies.[5-8] Nevertheless, little information is available at present concerning the chemical and histochemical alterations of the cardiovascular tissues in gargoylism. Although the incidence of typical gargoylism is low, the study of such patients may yield information that may permit the diagnosis in intermediate or atypical cases and may give further insight concerning the pathogenesis of other disorders of connective tissue.

It is the purpose of this report to record the clinical, pathologic, and histochemical findings in the cardiovascular system of a 5½-year-old child with an incomplete or atypical form of gargoylism who demonstrated severe mitral stenosis. The findings in this case are compared with similar clinical and pathologic observations in the literature.

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Case Report

The patient was a white boy known to have an atypical variety of congenital chondrodystrophy. He was first admitted to The Children's Hospital of Philadelphia at the age of 5 years for cardiac evaluation shortly after the discovery of a cardiac murmur and cardiomegaly associated with diminished exercise tolerance. He died 4 months later in acute congestive heart failure, a few hours after the onset of an intercurrent respiratory tract infection.

Both parents and a 3-year-old brother were normal and healthy. There had been no previous miscarriages. No history of consanguinity could be elicited; both maternal and paternal grandparents were Jewish and had immigrated from the same locality in eastern Europe.

The patient was born following an 8-month pregnancy which was terminated prematurely because of placenta praevia. Following the onset of vaginal bleeding, during the second month of pregnancy, the mother received daily oral "hormone" medication. The birth weight was 2,210 Gm.; there were no immediate neonatal difficulties. Physical examination in the nursery revealed small, square hands and feet, short upper extremities, and a position of extension of all extremities. No cardiac abnormalities were noted at this time. Roentgenograms of the long bones were reported to be normal. Incubator care was maintained for 3 weeks following which the patient was discharged weighing 2,515 Gm.

The patient fed poorly and gained weight slowly during the first few months of life. Beginning at the age of 2 months, episodes of "croup" occurred frequently. The infant seemed alert and showed no gross retardation in neuromuscular development

during the first year. Treatment with orthopedic appliances was instituted because of a dorsiflexion deformity of the feet. At the age of 11 months, the patient was hospitalized for 3½ weeks for treatment of diarrhea. Physical examination revealed short arms, wide and short feet and hands, and external rotation of the hip joints; the extremities were held somewhat rigid; and no teeth had erupted. Body measurements were as follows: height, 64.7 cm.; weight, 7,482 Gm.; head circumference, 41.3 cm.; abdominal circumference, 38.1 cm. The infant could sit alone while leaning forward and could grasp with his thumb and forefinger, but was unable to roll over from his back to his abdomen. Protein-bound iodine and I^{131} uptake measurements were normal. Roentgenograms of the upper extremities showed no ossification for the carpal bones. The spine, ribs, and clavicles were roentgenographically normal. The bones of the hands were grossly abnormal. The metacarpals and proximal phalanges were broad and short; the middle phalanges presented a broad base and were tapered at the distal ends. The bones of the forearms were short and somewhat thickened; the humeri were normal. Roentgenograms of the other lower extremities were normal except for the feet, which showed changes similar to those in the hands. The roentgenographic diagnoses were delayed epiphyseal ossification and dysostosis multiplex involving the hands and feet. After discharge from the hospital, physical and neuromuscular growth and development continued at a slow pace. The patient did not walk alone until the age of 2 years. Repeated attacks of "croup," especially during the winter months, were the only intercurrent illnesses.

Approximately 8 months prior to admission the patient began to show easy fatigability, cyanosis, and dyspnea that became progressively worse. Examination disclosed no cardiac murmurs. Upon re-examination a few weeks prior to admission to The Children's Hospital of Philadelphia, a loud precordial systolic murmur was noted for the first time by the same physician.

On admission to the hospital the patient had a high-pitched voice, seemed very small for his chronological age, and was of normal intelligence. The eyes were widely spaced; there was an unusual amount of hair on the face, particularly about the eyebrows (fig. 1). The body weight was 14.9 Kg.; the body length, 99 cm. The ratio of the trunk length to the length of the lower extremities was 1.27, which is within the normal range. The patient walked on his toes with his hips in external rotation. This "tiptoe" gait was due to contractures of both Achilles tendons. There were contractures in flexion of almost all major joints, with tightness

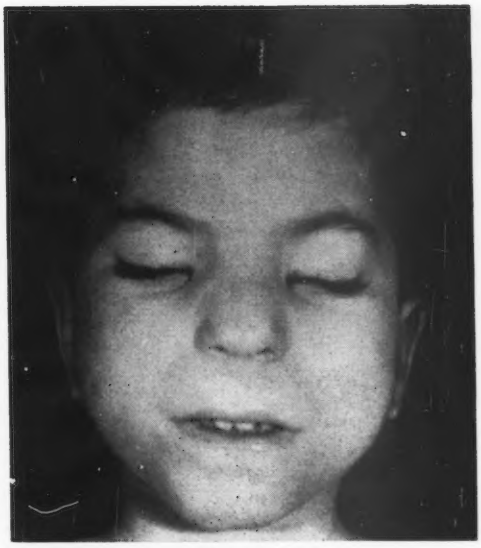

Figure 1

The head and face of patient at autopsy. Note the moderate degree of hypertelorism and the hirsutism of the face.

of the soft tissues, especially in the paraspinal region and about the thoracic cage. Examination of the eyes revealed endophthalmos and limitation of upper gaze, probably attributable to the abnormal anatomy of his orbits. No corneal opacities were noted, but slit-lamp examination was not done. The blood pressure in the upper extremities was 110/72, and the femoral and brachial pulses were normal. There was slight cyanosis of the mucous membranes and nailbeds, but no clubbing. The heart was enlarged to the left by percussion. The cardiac rate and rhythm were normal; the pulmonic second sound was accentuated and not reduplicated. A loud high-pitched systolic murmur of blowing quality, audible over the entire precordium, was loudest at the apex and was transmitted to the left axilla and to the back on the left side. In addition, a soft, high-pitched, early diastolic, blowing murmur was audible to the left of the upper sternum. This murmur had the characteristic quality of a murmur of semilunar insufficiency. No thrills were felt. The lungs were clear; the liver was palpable 2 cm. below the right costal margin in the midclavicular line. The remainder of the physical examination was unremarkable.

The blood studies on admission were normal except for a white cell count of 17,900 per $mm.^3$ and a serum albumin of 3.5 and globulin of 4.0 Gm. per cent. Serum cholesterol, cholesterol esters, cepha-

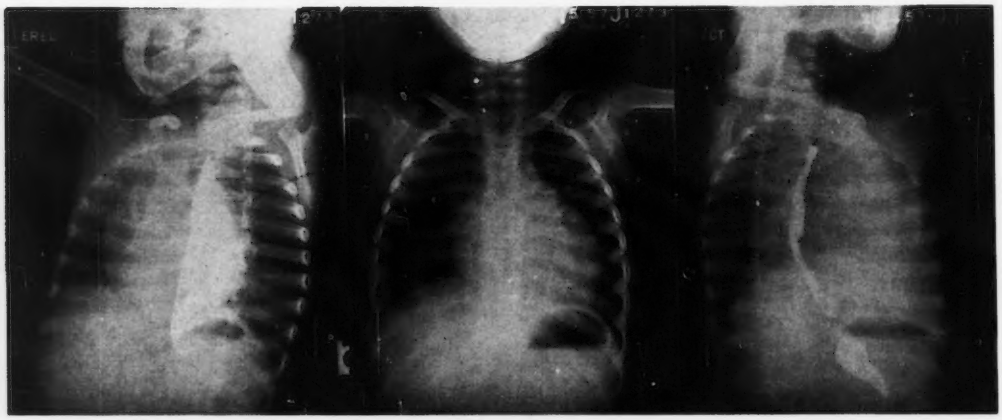

Figure 2

Roentgenograms of the chest. A moderate degree of cardiac enlargement of a diffuse nature is apparent.

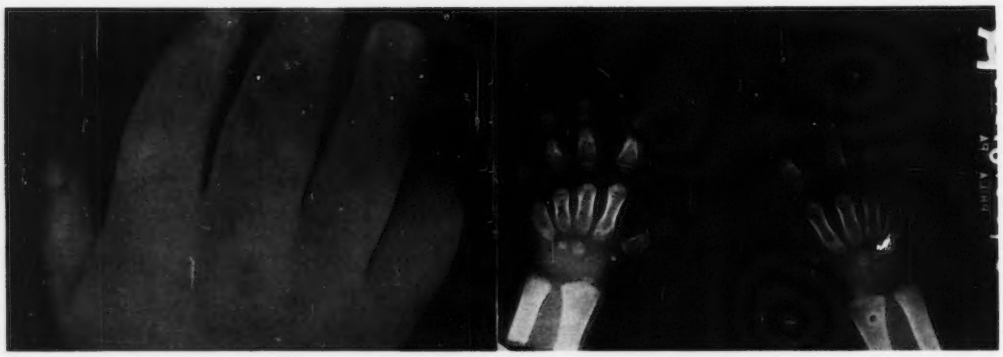

Figure 3

Left. *Photograph of right hand taken at autopsy. The hand is short and spade-shaped, the fingers taper toward the distal ends. The fifth finger shows moderate incurvation.* Right. *Roentgenogram of hands of the same patient, taken a few months prior to death, demonstrating the presence of only 2 ossified carpal bones, short and broad metacarpals, and the distal tapering of the phalangeal bones.*

lin flocculation, and thymol turbidity, erythrocyte sedimentation rate, protein-bound iodine, and streptococcal antibody titers were all at normal levels.

Roentgenographic examination revealed moderate generalized enlargement of the heart (fig. 2). The wrists demonstrated only 2 carpal bones, which placed the patient in the tenth percentile among 4-year-old boys. All of the phalanges and metacarpal bones were abnormally short. There was tapering of the distal ends of each phalanx of all digits, and a tendency toward tapering of the proximal ends of the metacarpals was noted (fig. 3). In the feet, 6 tarsal centers plus the second cuneiform were present, indicating a bone age of 4 years. The tarsonavicular center was not ossified. The head of the radius had not ossified in either elbow, but there was early ossification of the patella, both of which are 5-year-old centers. The hips and pelvis were normal. The dorsolumbar spine revealed wedging of the anterior body of the third lumbar vertebra, narrowing of the interspaces of the thoracic spine, and slight kyphosis.

The electrocardiogram (fig. 4) revealed right axis deviation and right ventricular hypertrophy. The P waves were tall and peaked, indicating atrial enlargement. A phonocardiographic tracing recorded at the cardiac apex demonstrated a short

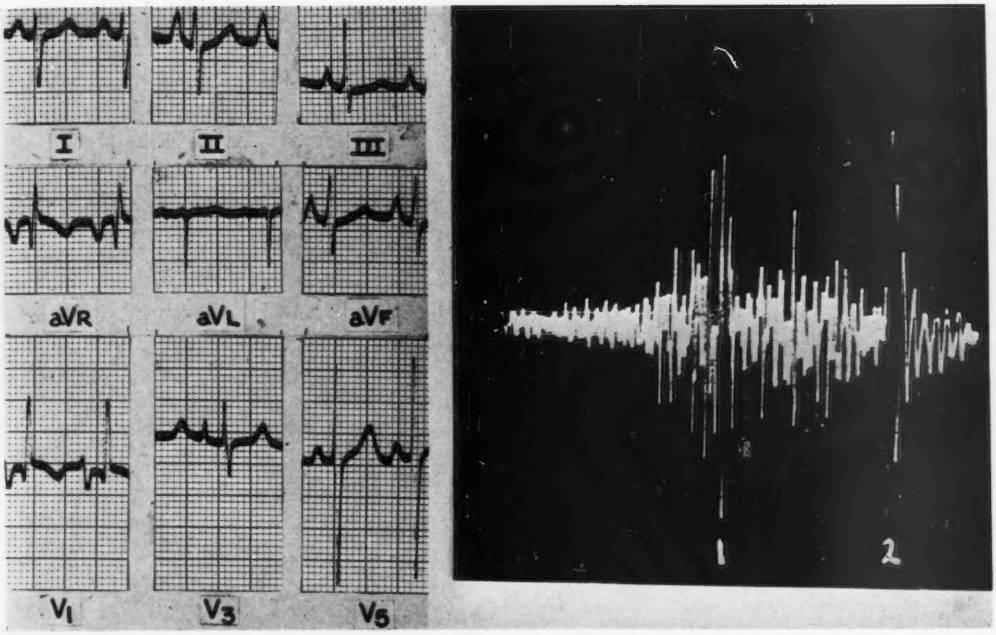

Figure 4

Left. *Electrocardiogram recorded 6 months prior to death.* Right. *Sound tracing recorded at the same time from the cardiac apex. The numerals 1 and 2 indicate the heart sounds.*

presystolic murmur in addition to the holosystolic murmur (fig. 4).

Because of signs of incipient congestive heart failure, the patient was digitalized. One month after admission he was discharged from the hospital on a maintenance dose of digitalis and prophylactic doses of oral penicillin. Oral diuretics were later added but provided little relief of symptoms. Four months later, the patient developed bradycardia and the dosage of digitalis was reduced. A few days later, however, signs of an upper respiratory tract infection appeared and were followed shortly by severe respiratory distress and tachycardia. On re-entry to the hospital the patient was greatly agitated, severely cyanotic, and appeared in acute congestive heart failure. He died several minutes after admission. The final clinical impression was an atypical form of gargoylism and congestive heart failure.

At postmortem examination the body weighed 14.5 Kg. and measured 99 cm. (heel to crown). The mucous membranes were moderately cyanotic and there was slight pitting edema over the lower extremities.

The heart weighed 250 Gm. The right atrium was normal in size with a wall thickness of 0.3 cm. and showed no abnormal communication with the left atrium. The tricuspid valve was normal except for a small, firm, white nodule measuring 1 by 1 mm. on the right atrial aspect of the anteromedial leaflet. The right ventricle was moderately dilated and hypertrophied, and was 1 cm. thick. The pulmonary valve was slightly thickened at its edges and measured 7 cm. in circumference. Two, small, thickened sclerotic areas were noted in the intima of the left pulmonary artery just proximal to its entry into the left lung. The ductus arteriosus was not patent. The left atrium was moderately dilated and hypertrophied; the wall was 0.5 cm. thick. The endocardium was moderately thickened. The mitral valve (fig. 5) was markedly thickened and was made up of a plicated, irregular mass in which the boundaries of the valve leaflets could not be delineated. The anteromedial aspect of this valve presented a small triangular opening into the left ventricle measuring 5 by 5 by 2 mm. A thin linear endocardial "jet lesion" was noted on the posteromedial wall of the left ventricle beginning at the mitral orifice and ending at the apex of the left ventricle. The left ventricle was smaller than normal in size and the muscular wall measured 0.9 cm. in thickness. The endocardium was moderately thickened. The papillary muscles of the mitral valve were drawn together and thickened and the

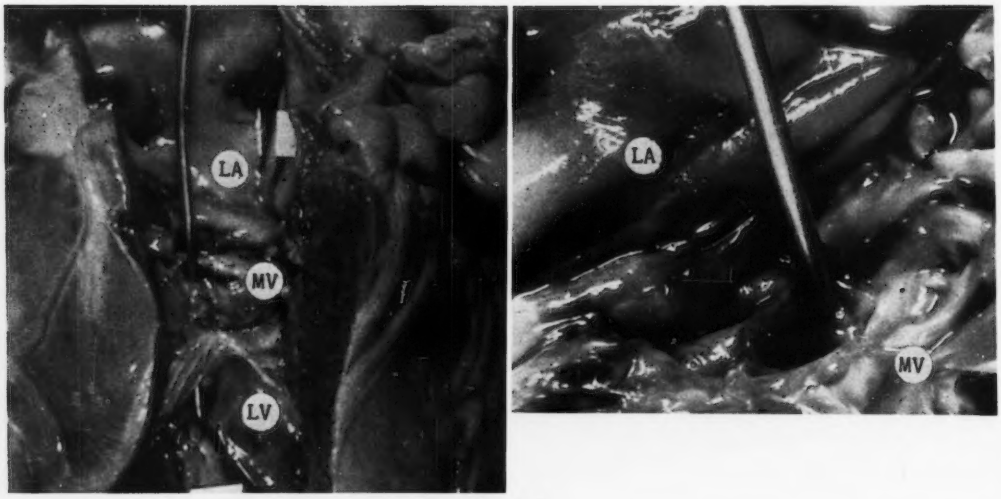

Figure 5

Gross specimen of the heart at autopsy. Left. *Section made through the left atrium, mitral valve, and left ventricle. Probe is seen to pass through orifice of the mitral valve. The endocardial thickening of the left atrium and left ventricle and the diffuse plicated thickening of the mitral valve are apparent.* Right. *Close-up view of the mitral valve and orifice. Note the markedly thickened valve leaflets, the fusion of the leaflets, and the thickened rolled edges adjacent to the small remaining mitral orifice. The letters LA, MV, and LV indicate the left atrium, mitral valve, and left ventricle, respectively.*

chordae tendineae were shortened and slightly thickened. The aortic valve, the coronary ostia, the coronary arteries, and the aorta were normal. The remaining endocardium, epicardium, and pericardium were not abnormal, and the myocardium of both ventricles was moderately firm in consistency.

All tissue sections were immediately placed in cold, neutral formalin and fixed at 4°C. Blocks of tissue from the heart included both atria, atrial appendages, ventricles, epicardium, and coronary arteries. Multiple sections were taken of all valves, including the annulus, chordae tendineae and papillary muscles. The tissues were embedded in paraffin and cut in serial sections from 4 to 6 μ in thickness. Routine staining procedures included elastica-Van Gieson, hematoxylin and eosin, Wilder silver, and phosphotungstic acid hematoxylin. The histochemical and enzyme digestion technics employed have been previously described.[9]

Microscopically, the heart showed moderate hypertrophy of the ventricular myofibers. Scattered focal clusters of pale-staining mononuclear cells were present in the interstitial connective tissue. These cells showed regular, oval nuclei with scattered chromatin and faint, granular, eosinophilic cytoplasm. An increase in collagen fibers was observed in the subendocardium, adjacent to the mitral and pulmonary valves. The endocardium of the left atrium, appendage, and left ventricle was thickened because of an increase in collagen and elastic fibers. The epicardium and pericardium showed no abnormalities.

The mitral valve (figs. 6 to 8) was thickened and distorted as a result of interlacing fascicles of collagen fibers arranged in dense bundles at the mitral sulcus and in the peripheral portions of the valve leaflets. These thickened fibers extended to the inner portion of the valve substance where they blended with an amorphous ground substance containing isolated, stellate-shaped mononuclear cells. The stellate-like cells were usually hyperchromatic with little or no cytoplasm; some appeared to have a perinuclear halo. The central core of amorphous material in the valve leaflets contained thin, widely separated argyrophilic fibrils and fragmented collagen fibers. The dense collagenization of the peripheral valve margins continued to involve the chordae and the upper portions of the papillary muscles. The changes noted in the pulmonary valve were due to an increase in collagen fibers in focal areas. The aortic and tricuspid valves were questionably altered.

Table 1 shows the histochemical studies employed in an attempt to characterize the alterations in the

Table 1

Interfibrillar Ground-Substance Reactivity of Mitral Valve

Mucopolysaccharide	
Toluidine blue	+++ (metachromasia)
Periodic acid-Schiff reaction	+++
Colloidal iron-periodic acid Schiff	diffuse staining
Alcian blue 8GS	+++
Testicular hyaluronidase*	no digestion
Lipid	
Sudan black B	negative
Nile blue sulfate	negative
Sudan IV	negative
Protein	
Aniline blue-chromotrope 2R	±
Ninhydrin-Schiff reaction	negative to ±
SH and S-S groups	negative

*Supplied by Worthington Biochemical Laboratories, New Jersey.

mitral valve. The amorphous ground substance was metachromatic with toluidine blue and gave a positive periodic acid-Schiff reaction. The negative Schiff control and phenylhydrazine-blocking reactions suggest that the periodic acid-Schiff positivity may be due to polysaccharide material. Alcian-blue dye was maximally present in areas that were metachromatic. The colloidal iron method was diffuse in staining the entire stroma of the valve a blue color. Testicular hyaluronidase failed to remove the substances responsible for the toluidine-blue metachromasia and alcian-blue positivity. Attempts to demonstrate neutral fat and phospholipids were negative. The results of the methods listed for the demonstration of proteins varied from negative to weakly positive.

Focal areas of endothelial proliferation were occasionally noted in the epicardial coronary arteries. Scattered, isolated intramyocardial arteries demonstrated subintimal collections of large mononuclear cells with pale, vacuolated or granular cytoplasm. The cytoplasm in these cells was faintly metachromatic and periodic acid-Schiff negative while the cell borders were clearly metachromatic and periodic acid-Schiff positive. The aorta was not unusual.

The lungs showed marked pulmonary edema and numerous heart-failure mononuclear cells in the alveolar spaces. Many of the pulmonary vessels showed moderate to marked degrees of medial thickening and intimal hyperplasia consistent with a marked degree of pulmonary hypertension.

There was a striking lack of microscopic alterations in the spleen and liver. The costochondral junction of the ribs (fig. 9) showed a marked disorganization of chondrocytes with a loss of normal architecture. Bone formation was irregular and incomplete.

Figure 6

Photomicrograph of the left side of the heart. Note the moderate endocardial thickening of the left atrium; the thickening of the mitral valve, and the marked thickening and shortening of the chordae tendineae. The coronary vessels in this section show no significant changes. Hematoxylin and cosin stain; × 40.

Discussion

The salient clinical findings in this patient include an atypical chondrodystrophy involving primarily the hands and feet, a peculiar facies, and liver enlargement. The pathologic findings in the heart and at the costochondral junctions are consistent with the diagnosis of an atypical or incomplete form of gargoylism. This case, we believe, is the second recorded proved instance of mitral stenosis associated with gargoylism and the first associated with an incomplete or atypical form.

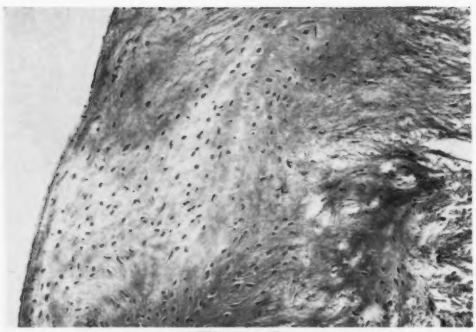

Figure 7

Photomicrograph of mitral valve. Colloidal iron-periodic acid Schiff; × 100.

Figure 8

Photomicrograph of the mitral valve. In this figure and in figure 7 note the marked increase of groud substance (smudgy dark gray areas between cells) and the increased number of large mononuclear cells with dark-staining nuclei and scant, pale-staining cytoplasm. Colloidal iron-periodic acid Schiff; × 450.

Descriptions of pathologic changes in the cardiovascular system in typical cases of gargoylism have been reported by Lindsay and associates,[1, 2] Strauss,[3] Craig,[4] Henderson et al.,[5] and Emanuel.[10] Although all tissue layers of the heart may be affected in varying degrees, the changes that occur in the valves, the endocardial lining of the chambers, and the coronary vessels are usually most prominent. Valvular involvement may be single or multiple; the mitral and aortic valves are more commonly affected than the pulmonary and tricuspid. Grossly, the valve leaflets are thickened and contain small nodulations along their free edges. The chordae tendineae also become thickened as well as shortened. Microscopically thickening and collagenization of the stroma of the valve leaflets occur with varying numbers of vacuolated mononuclear cells scattered within this stroma. The endocardial involvement is usually limited to the left side of the heart and may result in a degree of endocardial thickening similar to that observed in endocardial fibroelastosis.[11] Intimal proliferation and varying degrees of occlusion may occur in many of the larger and smaller coronary vessels.

The cardiovascular findings at autopsy in atypical or intermediate forms of gargoylism have been infrequently reported. Lindsay and co-workers[1] and Strauss and Platt[11] reported observations in 4½-month-old and 5-month-old infants, both of whom demonstrated the typical cardiac changes but none of the associated external manifestations considered typical of this disorder. Steen[12] described 3 cases, twins aged 8½ years and a brother age 7 years, who are apparently still living. These 3 children were classified as atypical cases and all had well documented clinical evidence of valvular alterations.

The alterations of cardiac tissue in our case were identical to those described in other cases of gargoylism and are the most severe changes yet described in the cardiac valves of an atypical or intermediate form of this disorder. Although the pathologic alterations in the heart and costochondral junctions of the ribs were consistent with a prolonged period of tissue reactivity, clinical evidence of heart disease was not noted in our patient until approximately 6 months prior to death. The paucity of typical large vacuolated mononuclear cells and associated connective-tissue changes in other organs such as the liver and spleen emphasized the variability of organ involvement in this disorder.

The basic abnormality in gargoylism, first demonstrated by Brante,[13] is apparently related to the accumulation of acid mucopolysaccharides in the connective tissue, reticuloendothelial, and parenchymal cells of various organs. The resultant tissue alterations prob-

ably depend upon the degree of "storage" of these materials and the secondary response of altered tissue metabolism in each organ involved. The existence of typical and intermediate forms of this disorder is probably related to the mode of inheritance of the basic defect, i.e., autosomal recessive or sex-linked recessive.

Although chemical and histochemical studies of the liver, spleen, and central nervous system tissues in various forms of gargoylism have been previously reported,[6-8] relatively little information of this nature is available with regard to the cardiovascular tissues. Previous histochemical studies on routine 10 per cent acid formalin-fixed tissues indicated that much of the accumulated mucopolysaccharide material was lost and most of the studies demonstrated primarily the lack of accumulation of glycogen and fat. Recently Strauss and Platt[11] demonstrated metachromatic granules in the large connective-tissue mononuclear cells and reported the removal of this metachromasia by the action of an unspecified type of hyaluronidase.

Our studies demonstrated a small amount of metachromatic material in the mononuclear cells of the connective-tissue stroma in the mitral valve leaflets. In addition, the alterations in ground substance of the valve were due primarily to the accumulation of acid mucopolysaccharide material with varying degrees of collagenization of this material. Repeated attempts to remove the metachromatic components with crude testicular hyaluronidase were totally unsuccessful. Metachromasia of amyloid is also known to be resistant to hyaluronidase digestion, probably because of the presence of a sulfated acid mucopolysaccharide.[14] The staining technics employed are not specific and final clarification of these histochemical interpretations must await data from more direct biochemical analyses. Nevertheless, the evidence presented by these studies suggests that the basic tissue alterations in the cardiovascular system are similar to the findings by chemical analyses in other organs and support Brante's original contention that gargoylism is a generalized "mucopolysaccharidosis."

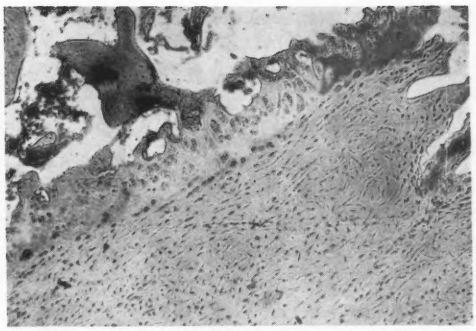

Figure 9

Photomicrograph of costochondral junction. There is general disorganization of the cartilage plate associated with decrease in chondrocytes, blunting of the bone trabeculae, and focal deposition of acid mucopolysaccharide material. Colloidal iron-periodic acid Schiff; × 100.

In an attempt to determine the sequential development of clinical cardiac findings in cases of gargoylism, 29 case reports that included autopsy descriptions of the heart were reviewed.[1-5, 7, 10, 11, 15-25] This review did not provide adequate clinical data for a significant clinicopathologic evaluation of the cardiac involvement in the various forms of this disorder. Since all layers of the heart may be affected to varying degrees at any one time, the clinical cardiac findings associated with gargoylism will depend on the cumulative extent of the particular tissue layers of the heart affected at the time of study. Nevertheless, it may be of some significance that the most frequent cardiac alterations in gargoylism are those involving the valvular structures and that the order of frequency of involvement and the resultant changes of these valves resemble closely those found in rheumatic heart disease. Thus, a sequence of clinical cardiac events similar to those occurring in progressive rheumatic heart disease might be anticipated in patients with gargoylism. The clinical findings in our case tend to substantiate this concept but the detailed clinical analysis of many more cases will be required for confirmation.

Cardiac involvement may occur with little clinical evidence of other organ involvement considered typical of gargoylism, and this disorder should be considered in the differential diagnosis of valvular heart disease in childhood. The recent findings of Meyer et al.[26] and Dorfman and Lorinez[27] of increased urinary excretion of chondroitinsulfuric acid B and heparin monosulfuric acid in patients with gargoylism may aid in establishing the diagnosis of incomplete forms of this disorder.

Summary

The clinical and pathologic findings in a 5½-year-old white boy with fatal, atypical gargoylism and severe mitral stenosis are presented. Histochemical studies of the cardiac alterations in this patient are outlined and discussed. These alterations in the cardiac tissue suggest that the accumulation of acid mucopolysaccharides in the connective tissue of the valve leaflets leads to the formation of collagen fibers and sclerosis. The basic tissue alterations in the heart are similar to those reported to occur in other organ systems in this disorder and support the concept that gargoylism is a generalized "mucopolysaccharidosis." Because severe cardiac involvement may occur in this syndrome in the absence of many of the other clinical manifestations of this disorder, gargoylism should be included in the differential diagnosis of valvular heart disease in childhood.

Summario in Interlingua

Es presentate le constatationes clinic e pathologic in un puero de racia blanc de 5½ annos de etate con atypic mortal chondrodystrophia e sever stenosis mitral. Studios histochimic del alterationes cardiac in iste patiente es delineate e discutite. Iste alterationes in le histos cardiac pare indicar que le accumulation de mucopolysaccharidos acide in le histos conjunctive del cuspides valvular resulta in le formation de fibras collagenic e de sclerosis. Le basic alterationes del histos cardiac es simile a illos reportate pro altere systemas de organos in iste disordine e supporta le conception que chondrodystrophia es un "mucopolysaccharidosis" generalisate. Proque sever affectiones cardiac pote occurrer in iste syndrome in le absentia de multes del altere manifestationes clinic de iste disordine, chondrodystrophia deberea esser includite in le diagnose differential de morbo valvular del corde in le pueritia.

Acknowledgment

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Forthcoming Articles

Hypertension and Vascular Disease. Harry Goldblatt

Familial Muscular Subaortic Stenosis: An Unrecognized Form of "Idiopathic Heart Disease" with Clinical and Autopsy Observations. Lawrence B. Brent, Akio Aburano, Don L. Fisher, Thomas J. Moran, Jack D. Myers, and Jape W. Taylor

Critical Evaluation of Electrocardiographic Diagnosis of Ventricular Hypertrophy Based on Autopsy Comparison. Bertram J. Allenstein and Hiroyoshi Mori

Heart Disease and Filtrable Viruses. John M. Pearce

Social Aspects of Cardiovascular Rehabilitation. Marvin C. Becker, Wayne Vasey, and Jerome G. Kaufman

Goitre Plongeant

Intrathoracic Goiter Demonstrated by the Valsalva Maneuver

By HENRY T. PERKINS, JR., M.D., HENRY D. MCINTOSH, M.D., AND JOHN P. BOINEAU, M.D.

The diagnosis of an intrathoracic goiter can, on occasion, be difficult to confirm. The Valsalva maneuver was found useful in making this diagnosis in 2 patients whose case histories are reported. Such goiters are termed plunging goiters. The phenomenon is discussed and the use of the Valsalva maneuver in demonstrating such lesions is emphasized.

A PATIENT was found to have a mediastinal mass on a routine chest x-ray. The nature of the lesion, an intrathoracic goiter, was determined only after several diagnostic procedures. In retrospect, the correct diagnosis could have been made during the initial physical examination by means of the Valsalva maneuver. A second patient was recently seen with a similar lesion. The Valsalva maneuver again was useful in confirming the diagnosis of an intrathoracic goiter. Because of the rarity of the phenomenon and because this maneuver can easily be employed during an examination of patients with undiagnosed mediastinal lesions, these cases are presented.

Case Reports

Case 1

E. M. D., a 58-year-old Negro woman was admitted to the Duke Medical Center in July 1958 for evaluation of a mediastinal mass demonstrated on a routine chest x-ray 1 month prior to admission. She had had several routine chest x-rays during the preceding 5 years but had not previously been informed of any abnormality.

The patient had been asymptomatic except for increasing dyspnea on exertion during the 3 months prior to admission. She denied cough, hemoptysis, or chest pain. She had never observed a goiter, nor had she experienced symptoms suggestive of thyroid dysfunction.

The physical examination was essentially noncontributory except for the thyroid gland, which was twice normal size. Palpation of the gland revealed no evidence of substernal extension. No bruit or thrill was present over the gland. There was no percussion dullness over the upper sternum with the neck flexed or hyperextended, nor was any obvious substernal component noted to appear during either of these procedures.

Routine laboratory studies of blood, urine, and stool were normal. Serologic test for syphilis and skin tests for tuberculin and fungi were negative. The basal metabolic rate was +12 per cent. The electrocardiogram was unremarkable.

Films of her chest showed, besides a somewhat tortuous aorta, a large, rounded, well-circumscribed mass in the right superior mediastinum with minimal deviation of the trachea and esophagus to the left (fig. 1*A*). At fluoroscopy, shallow pulsatile-like movements were noted to involve the mass, possibly the result of transmitted pulsations from surrounding vessels. During the Valsalva maneuver, the mass appeared higher in the superior mediastinum and seemed to decrease in diameter (fig. 1*B*). On the lateral film of the chest during the Valsalva maneuver, the mass appeared to be separated about 0.5 cm. from the arch of the aorta. Consequently, the diagnosis of an aneurysm of the innominate artery was entertained along with certain other diagnoses, including intrathoracic thyroid.

The latter diagnosis was proved by a radioactive iodine uptake study with scanogram, which revealed a 40 per cent iodine uptake over the region of the right apex and superior mediastinum. Angiocardiography demonstrated no abnormality of the cardiac chambers or the aorta. The innominate artery was well visualized but the mediastinal mass was never opacified.

The demonstration of the intrathoracic goiter was best accomplished by having the patient perform a Valsalva maneuver, not in the darkness of the fluoroscopy room, but on the ward. During this maneuver, the intrathoracic mass protruded into the anterior neck, to the right of the midline, accounting for the apparent decrease in size of

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the lesion during the Valsalva maneuver at fluoroscopy (fig. 2). On relaxing with resumption of normal respirations, the mass slipped back into the chest, and at that time, there was again no visible or palpable evidence of substernal goiter.

Surgery to remove the intrathoracic thyroid was strongly advised but refused.

Case 2

J. B. D., a 70-year-old white man was admitted to the Durham Veterans' Administration Hospital in February 1959, following an episode of severe anterior chest pain with fever, nausea, and vomiting. His past history included treatment for an acute myocardial infarction and mild diabetes.

The blood pressure was 180/80. The thyroid gland was slightly enlarged and somewhat nodular. An ill-defined mass was just palpable in the right supraclavicular and sternal areas. The mass appeared to arise from within the chest. Examination of his chest and heart was noncontributory. All peripheral pulsations were easily felt.

Admission laboratory data revealed an initial leukocytosis and glycosuria.

It was thought that the patient was suffering from arteriosclerotic heart disease and diabetes mellitus. Several electrocardiograms failed to demonstrate the changes of an acute myocardial infarction.

The supraclavicular mass at first was thought to represent a neoplastic process from the right lung. The chest x-ray, however, revealed not only a superior mediastinal mass extending toward the right apex but tracheal deviation to the left (fig. 3), and the mass was noted during fluoroscopy to move on swallowing. The diagnosis of intrathoracic goiter was further suggested when it was observed that on mild straining, the mass easily came into view, and during the Valsalva maneuver the firm mass protruded far up into his right anterior neck (fig. 4). It was also noted that deep inspiration would suck the mass back into the chest so as to render it entirely inconspicuous. No bruit or thrill was noted over the anterior chest or over the extruded mass.

The basal metabolic rate was +39 per cent. A radioactive iodine uptake determination with a scanning procedure revealed a 13 per cent uptake in 24 hours. There was no uptake over the intrathoracic mass.

On further questioning, the patient stated that he had observed this phenomenon of the mass extruding into his neck on straining for 3 years. He had never noted a cervical goiter, however. During the same period, he had experienced sensations of choking and dyspnea on lying down which he would relieve by dorsiflexing his neck as far posteriorly as possible. He had also experienced dysphagia but denied a chronic cough or wheezing.

His hospital course was complicated by an acute thrombosis of the left popliteal artery, which was

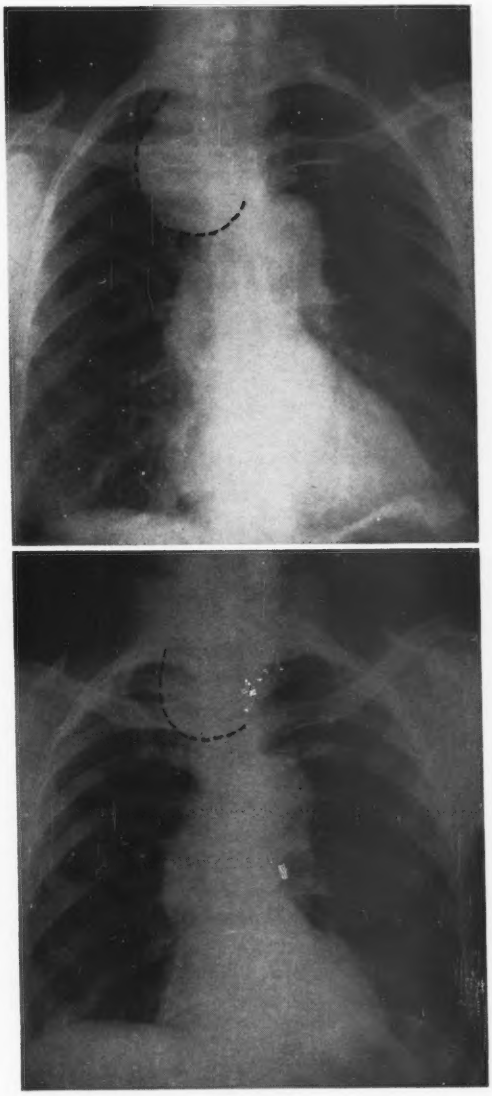

Figure 1

A. Top. *Case 1. Roentgenogram of the chest showing the large mass projecting from the right superior mediastinum.* B. Bottom. *Roentgenogram of chest during Valsalva maneuver showing the upward displacement of the mass. Calcification is now visible to the left of the mediastinum.*

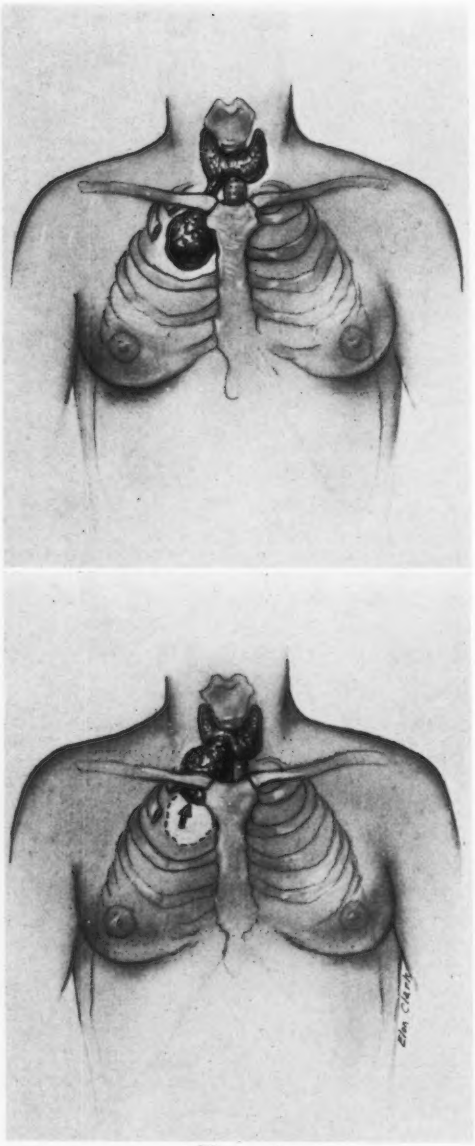

Figure 2

A. Top. *Diagrammatic representation of the intrathoracic goiter of the first case presented.* B. Bottom. *Diagrammatic representation of the same goiter in its cervical position during a Valsalva maneuver.*

treated surgically. Because of this complication as well as his other cardiovascular problems, surgical removal of the intrathoracic goiter was not considered advisable at that time.

Discussion

The incidence of goiters whose major part extends substernally varies from one series to another. In 1,265 thyroidectomies, Wakeley and Mulvany[1] reported 17 of this type. McCort[2] reported 28 such goiters in 908 thyroidectomies in which at least the major part lay within the thorax. Lahey[3] reported over 1,300 intrathoracic goiters out of 13,000 patients operated upon for goiter. In these cases, the goiter extended to or below the arch of the aorta.

Less common, however, are totally intrathoracic goiters. Of the large series of Wakeley and Mulvany,[1] only 3 goiters could be considered entirely intrathoracic. Eight of the 28 cases of intrathoracic goiter in the series of McCort[2] were completely intrathoracic. Of the 24 cases presented by Ellis, Good, and Seybold[4] of intrathoracic goiter removed by routes other than the usual cervical incision, 6 cases had had no palpable cervical thyroid gland and had no prior history of thyroidectomy.

Rarer still is the intrathoracic goiter that can reappear in the neck during increased intrathoracic pressure. Wakeley[5] and Clute and Lawrence[6] credit Malard[7] with having described this entity, naming it *goitre plongeant*. Wakeley reported 2 cases in a series of 1,300 goiter operations. Clute and Lawrence[6] discussed the condition but did not add a case of their own to the literature. Slobodkin[8] described an elderly man whose goiter appeared in his neck on coughing or straining and suggested the term "bobbing" goiter to be more appropriate. Shocket and Hudson[9] described a 56-year-old patient who was studied because of a mediastinal mass. When he strained during a bronchoscopy, a cervical mass appeared. This occurred with a Valsalva maneuver also, and the diagnosis of goiter was confirmed by radioactive iodine study and by surgery.

The lobes of the thyroid gland occupy a space in a fascial plane entering directly into the superior mediastinum. Because of factors such as respiration, swallowing, neck flexion and gravity, there may be a tendency for certain thyroid goiters to descend into the ches

nd, eventually, to become permanently edged within the cavity by growth in ize.[3, 8, 10] In some cases, prolonged coughing nd straining may exert enough force to exrude the intrathoracic gland back into the neck.

The symptoms caused by the plunging goier are usually referable to its intrathoracic position and therefore similar to the usual intrathoracic goiter. Both patients of Wakeley had noted cervical masses which, on disappearing into the thorax, would cause symptoms of shortness of breath and cough which would be relieved only by expelling the mass by violent coughing. In one case, distention of the neck vein was noted following the disappearance of the goiter into the thorax.[5] Slobodkin's patient with a bobbing, intrathoracic goiter complained of difficult breathing on lying down and of being awakened from his sleep by coughing and choking spells. This patient had a pharyngo-esophageal diverticulum in addition to the goiter.[8] Interestingly, the same patient had been advised, some 35 years previously, to have a goiter removed, although no cervical goiter was evident to the author at the time of his examination. Shocket and Hudson's patient had complained only of exertional dyspnea.[9]

The preoperative diagnosis of intrathoracic goiter can often be made on radiographic evidence. McCort[2] considered the finding of tracheal displacement, esophageal compression or displacement, upward movement of the mass on swallowing, and calcification within the lesion to be useful radiologic evidence. Fluoroscopy can be misleading, however. The series of Ellis, Good, and Seybold,[4] for instance, included 2 cases where visible pulsation of the tumor was noted, although it was not clear whether this was expansile or transmitted movement. They postulated that a highly vascular tumor might show expansile movement. This possibility was further suggested by the patient of Codington and Cowley[11] whose intrathoracic goiter simulated a saccular aneurysm of the aorta when it took up contrast material directly from the aorta during angiocardiography. Radioactive iodine

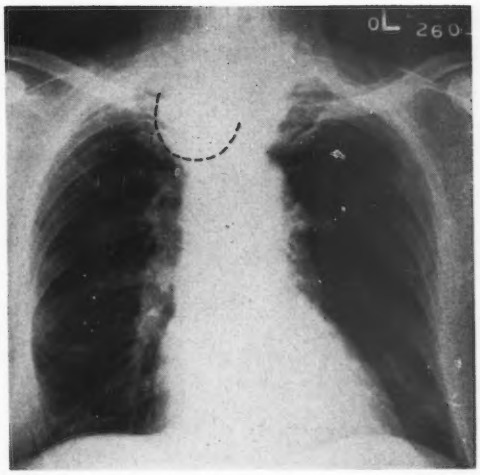

Figure 3

Case 2. Roentgenogram of the chest showing a superior mediastinal mass extending toward the right apex.

uptake studies are sometimes helpful in the diagnosis of intrathoracic goiter but when negative cannot, of course, be used to rule out such a lesion. McCort[2] emphasized the finding of a cervical goiter in suggesting the diagnosis of intrathoracic goiter in patients with undiagnosed tumors of the mediastinum, having demonstrated some degree of thyroid enlargement in 20 of the 28 patients in his series. The history of a cervical goiter that has disappeared from the neck without surgery should also be sought.

Several additional points should be emphasized regarding the diagnosis of intrathoracic goiter. The history of a previous cervical goiter may not always be elicited, nor might the patients have noticed the appearance of a cervical mass at any time on straining or coughing. Although probably present, examination of the cervical gland may not always yield the palpable projection leading substernally to suggest the diagnosis. Finally, the ease and rapidity with which the Valsalva maneuver can be employed warrants its use in the examination of patients presenting with mediastinal lesions as a physical sign, which could suggest the diagnosis of goiter. It is obvious that a negative test would not rule

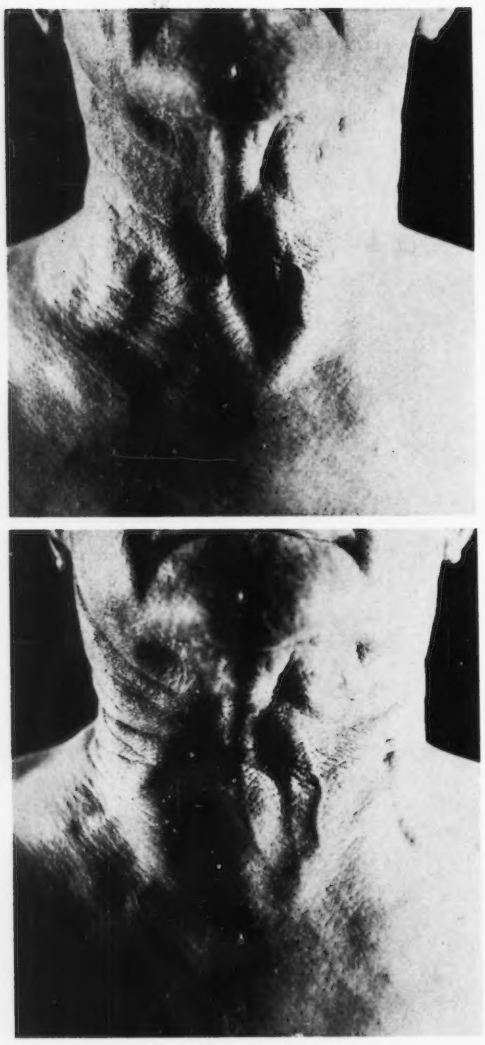

Figure 4

A. Top. *Case 2. Photograph of the anterior neck of the patient before the Valsalva maneuver.* B. Bottom. *Photograph of the same patient during Valsalva maneuver. A mass is seen protruding far up into the neck, to the right of the midline.*

out the diagnosis of intrathoracic goiter. However, the appearance of an intrathoracic mass in the neck must always suggest goiter. The likelihood that a mediastinal lesion of another etiology might appear in the neck during the Valsalva maneuver is remote indeed.

Summary

Two patients with *goitre plongeant* are presented.

The incidence, mechanism, symptomatology and diagnosis of the condition are discussed.

The use of the Valsalva maneuver as an aid in the diagnosis of intrathoracic goiter is emphasized.

Summario in Interlingua

Es presentate le casos de duo patientes con struma intrathoracic del typo designate depost Malard (1859) como *goitre plongeant.*

Le incidentia, le mechanismo, le symptomatologia e le diagnose del condition es discutite.

Es sublineate le utilitate del proba de Valsalva como adjuta in le diagnose de struma intrathoracic.

Acknowledgment

We wish to express our appreciation to Mr. Elon Clark, of the Duke Medical Illustrations Department, and to Mrs. Pat Price for their patient assistance in the presentation of this paper.

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SYMPOSIUM ON CONGESTIVE HEART FAILURE

Hemodynamic Aspects of Congestive Heart Failure

By L. N. KATZ, M.D., H. FEINBERG, PH.D., AND A. B. SHAFFER, M.D.

The 3 articles in this issue on congestive heart failure comprise the first of 10 contributions on this subject. The remaining 7 articles will be published in the February and March issues.—EDITOR.

IN this discussion of the hemodynamic aspects of congestive heart failure, we propose to review clinical observations and the results of animal experiments. On this basis, our concepts concerning the sequence of changes in the heart that lead to congestive heart failure are summarized.

It is well known that congestive heart failure, while starting as a deficit of myocardial performance, ends as a syndrome in which many organs, particularly the kidney, lungs, and liver, are altered, as are many homeostatic functions. Certain aspects of this subject have been considered in previous reviews,[1-9] or are dealt with in other sections of this symposium. In the present review, we will confine ourselves primarily to the heart, and especially to those of its alterations, physical or chemical, that are recognized as having some possible bearing on the disturbed hemodynamics of congestive heart failure.

Congestive Heart Failure Defined

The function of the heart is to eject the blood that is returned to it. It is obvious, then, that the heart is as much the servant of the circulation as its master. It is often difficult or impossible, in man, to separate clearly the primary hemodynamic manifestations of a diseased heart muscle from those of a primarily compromised circulation, or from secondary circulatory adjustments.

An inadequate circulation (*circulatory* insufficiency or failure) is manifest by a low cardiac output in relation to the current needs of the body, or by the accumulation of undue quantities of blood in the systemic or pulmonary venous system, or both (*congestive* circulatory failure). On the other hand, the term heart failure in this report is considered to be synonymous with *myocardial* failure, which implies as its starting point an inadequate myocardial contraction with reference to the circulatory load. It should be clearly recognized that there are many extracardiac causes of circulatory failure and that myocardial failure is only one of the cardiac abnormalities, structural or functional, which may result in circulatory failure.

Just as myocardial failure is not a *necessary* condition of circulatory failure, so the absence of circulatory failure is no guarantee of an uncompromised myocardium. A normal circulation may be maintained by an augmented cardiac effort, with a resulting decrease in cardiac reserve.

Myocardial effort is directed toward meeting 2 types of load. The heart must accelerate

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the movement of the blood returning to it (input or diastolic load) and must, at the same time, overcome the resistance to its ejection (resistance or systolic load). The normal myocardium responds to an increased load in a variety of ways, depending on the type of load, its magnitude, and its rate of development. Tachycardia and dilatation represent the more acute, "crude" adjustments to an increased load. Dilatation is also a consequence of chronically increased diastolic load. Hypertrophy, on the other hand, represents a more gradual response, and is most marked in instances of chronically increased systolic load. More subtle are the processes within the heart muscle itself, for the most part neurogenically or hormonally conditioned, which determine the behavior of the myocardium from beat to beat (see below).

"Myocardial reserve" relates cardiac effort, however measured, to the maximum effort of which the heart is capable with respect to the particular aspect considered. Increased work loads obviously narrow the gap between existing and maximal efforts, while myocardial disease narrows the gap by reducing the possible effort maximum. The concept of cardiac reserve has limited usefulness clinically, however, since it encompasses so many factors and there is no standard way of applying it. For example, hypertrophy of a ventricle increases cardiac reserve in one sense, but reduces it in another, since as hypertrophy develops, there is less potential for further hypertrophy.

The following incomplete tabulation serves to illustrate by means of clinical examples the relationship of circulatory to myocardial failure. Circulatory failure results from

1. Interference with systemic venous return due to factors remote from the heart (such as hemorrhage, peripheral vascular collapse, shock), or in the heart region (such as pericardial tamponade, constrictive pericarditis, tricuspid stenosis). Congestion is generally a feature of the latter group but not of the former. Myocardial failure is not a necessary concomitant of these states.

2. Interference with the pumping or filling mechanics of the ventricles due to some architectural abnormality. This need not be associated initially with myocardial failure (viz., acute pulmonary edema due to mitral stenosis), but ultimately leads to circulatory failure on the basis of failure of one or both ventricles (e.g., semilunar valvular stenosis or insufficiency, mitral stenosis or insufficiency, tricuspid insufficiency, arterial hypertension of either circuit, pulmonary emboli or thrombosis). In all these conditions, forward flow through the arteries, though initially normal, is small in relation to the amount of effort that the heart must exert.

3. Primary diseases of the myocardium that lead to muscle failure. These may be due to localized loss of substance (as in myocardial infarct), or to diffuse involvement (as in myocarditis, amyloidosis).

4. Any stimulus to high output of one or both ventricles, be it hypervolemia (as in excessive intravenous infusion of blood or other fluid, and possibly acute glomerulonephritis), drastic reduction in peripheral vascular resistance (as in systemic A-V fistula, beriberi, hyperthyroidism, Paget's disease), hypoxia (as in anemia, chronic cor pulmonale), or possibly a direct metabolic effect on the myocardium (as might occur in hyperthyroidism). Also included in this group are uncomplicated congenital cardiovascular malformations with large left-to-right shunts. In these conditions, systemic flow may be reduced while pulmonary flow is increased, and the diastolic load to one or the other ventricle is markedly increased (the right ventricle in interatrial septal defect, the left ventricle in patent ductus arteriosus). With the exception of the last-mentioned conditions, the obvious hemodynamic manifestations of "high output" circulatory failure are by definition congestive only, at least initially. However, the presence of a high cardiac output must not be taken to imply that flow to *all* organs, e.g., the kidneys, is necessarily high, or even normal. The controversy continues as to whether myocardial failure per se in man may occu-

simply on the basis of an "overwhelming" diastolic load. Certainly some of the conditions leading to high output circulatory failure have an additional primary deleterious effect on the myocardium itself (as in the hypoxic group, beriberi, and possibly in acute glomerulonephritis and hyperthyroidism), and then myocardial failure may be precipitated much as it may be under the stimulus to high output of physical exercise. In other instances (as in "iatrogenic" hypervolemia, arteriovenous fistula, "malignant" ductus arteriosus), the only effect of the underlying process on the myocardium is hemodynamic, and it would seem unlikely in such instances that there must invariably be a separate myocardial disease. Thus, it is by no means ruled out that these "high output states" can lead to congestive heart failure, as defined, insofar as they may give rise to a diastolic load with which even a normal ventricle cannot cope. Here congestion may be in part the cause and in part the result of myocardial failure.

It is obvious that in a given clinical condition, the causes of *circulatory* failure may be multiple. Further, compensatory mechanisms within the heart itself (such as inapparent dilatation) or at the periphery (such as slightly increased oxygen extraction) may prevent myocardial failure from being manifest in its earliest stages.

A given entity may not fit into a single group. For example, the behavior of endocardial fibroelastosis in a given case may classify it in any of the first 3 groups. Functional derangements of the heart or circulation (vaso-vagal syncope, rapid heart action, cardiac arrest) also may result in circulatory failure in the absence of myocardial failure.

These groups constitute a crude therapeutic classification. There is no doubt that the best treatment of any hemodynamic abnormality is a direct attack on the primary cause. This is the only effective approach to the conditions in group 1, while measures (such as digitalis) aimed at supporting the compromised myocardium may be very effective in groups 2 and 3. The clinical response to such measures is characteristically erratic in the heterogeneous group 4.

Congestive Heart Failure in Man

Considerable knowledge concerning the heart and circulation in health and disease has been obtained through the use of newer technics such as cardiac catheterization. It is, of course, not possible to explore the human heart with the same precision, under stable conditions, or with the opportunity to alter these conditions, as is the case in animal experiments. Sometimes the imperfections and limitations of the methods employed in man have been ignored or minimized in attempts to evaluate the basic importance of the findings. While there is little reason to doubt the validity of most observations, their implications are limited with regard to basic understanding of myocardial function in health and disease because of the inadequate methodology. On the other hand, such studies have to some extent indicated the necessary direction of more basic work.

Cardiac catheterization of the right side of the heart, and, to a lesser extent, of the left, has contributed to knowledge in this field insofar as it has made possible the adequate measurement of pressures and *mean* flows in the cardiovascular system of normal individuals and patients in heart failure. Such measurements have been made with the subject at rest, on exercise, under the influence of certain drugs (e.g., epinephrine), and during certain other procedures such as rapid intravenous infusion or venesection. Many of these studies have been attempts to investigate the validity of Starling's law in the intact human being.

Hemodynamic studies of normal individuals at rest and exercise[10–12] have indicated the normal range of minute and average stroke outputs and the expected low levels of right and left ventricular diastolic pressures (the latter measured via the pulmonary arterial wedge). There has been, in general, no consistent relationship between ventricular diastolic pressure changes and alterations in stroke volume, heart rate, minute output, or

external work (per minute or per beat).* One study, in which intrathoracic pressure was measured, thus allowing determination of true right ventricular diastolic pressure, demonstrated a direct relationship between this pressure, as a measure of right ventricular filling pressure, and cardiac output as an index of myocardial effort.[14] The effects of rapid intravenous infusion or venesection on the relationship of ventricular diastolic or atrial pressure to cardiac output or external work have not been consistent from study to study.[10, 15-18] Epinephrine, however, was shown, many years ago, to alter cardiac output independently of right atrial pressure.[10, 15]

The more gross hemodynamic aspects of congestive heart failure, as in groups 2 and 3 above, have also been revealed by catheterization. The measurable hemodynamic expressions of poor myocardial contractility are essentially those of circulatory insufficiency, i.e., high ventricular diastolic pressure (congestion with the cause localized to one or both ventricles) and diminished cardiac output. On exercise, diastolic pressure rises further while minute output (as measured) may rise slightly, remain stationary, or even fall.[19, 20] Of course, circulatory insufficiency, not demonstrable at rest, may become apparent on exercise. When cardiac output is determined by the Fick principle, inadequacy in congestive heart failure is characterized by a large A-V oxygen difference relative to the level of oxygen consumption, indicating that the tissues compensate for the reduced rate of flow by greater oxygen extraction per unit of available blood. Low cardiac output may also be a feature of myxedema, but here oxygen consumption is often low and the A-V oxygen difference at rest and exercise is *not* relatively widened,[21, 22] indicating that flow remains proportional to the oxygen demands of the body.

*The classical parameters of external work are minute cardiac output and blood pressure in the great vessel leaving the ventricle under study. Stroke work (average) is external work per minute divided by heart rate. The work done in imparting kinetic energy to the ejected blood is usually neglected.[13]

Such studies have also revealed that ventricular end-diastolic pressures well above the normal range may be associated with marked ventricular hypertrophy (as in aortic or pulmonic stenosis) in the absence of other evidence of heart failure.[23, 24] It is postulated that this is due to marked thickening of the ventricular wall which has altered the distensibility of the relaxed chamber.

Circulatory alterations caused by rapidly acting digitalis preparations have been studied in cases of congestive heart failure. In general, right (and indirectly determined left) ventricular diastolic pressure falls (reducing congestion) while cardiac output rises and the heart rate (inconstantly) slows. There is, however, no unanimity among the various observers about the order in which these changes occur. Sometimes, there has been a fall in venous pressure followed by a rise in cardiac output[25] suggesting an effect of digitalis on the venous system similar to venesection, leading to a fall in pressure and venous return so as to "*decompress*" an incompetent ventricle.[26] In other instances, cardiac output rises without change in venous pressure, or with a subsequent fall in this pressure,[27, 28] indicating the more accepted myocardial effect of digitalis. Venous pressure may also fall without a rise in cardiac output.[29] The heart rate may be slowed as a primary effect of digitalis (particularly in atrial fibrillation), or slowing may reflect improvement in the myocardium.

Increased cardiac output with or without increased ventricular diastolic pressures (directly or indirectly measured) has been demonstrated in many of the "high output" states.[30-37] In contrast to groups 2 and 3, high venous or atrial pressures, when present, are not characteristically altered by digitalization.[38] In one study, digitalis was found to have an effect in patients with large (apparently dilated) hearts who were clinically not in failure, similar to its action on the normal heart.[39]

In brief, then, while low cardiac output, dilated ventricular chambers, and high ventricular diastolic pressures, collectively

characterize myocardial failure, each can exist alone under conditions in which myocardial failure is apparently absent.

Such observations are valuable but present a very incomplete picture. There is the difficulty of assessing the alterations in cardiovascular pressures against the background of respiratory variations in intrathoracic pressure. Further, the observations are only spot samples in a long drawn-out process, as obtained in the closed circulation of an intact human being. Again, the possible beat-to-beat changes in stroke volume and the possible changes in stroke volume of one ventricle independently of the other cannot be detected in man. Consequently, it has, for example, so far been impossible to record directly the momentary disparity in output between the 2 ventricles that is presumed to play a part in the development of pulmonary congestion in left ventricular failure, or to lead to its relief on treatment.

Basic to a full understanding of the behavior of the normal or failing heart as a pump, is knowledge of (1) the indices of myocardial performance or effort, (2) the factors influencing myocardial effort, and (3) the energy cost of such effort. As mentioned, clinical work directed to these matters has been dominated by the concept that relates cardiac effort to ventricular end-diastolic volume, as enunciated by Starling and his followers. Thus, external work, per minute or average per stroke, has so far been the only index of myocardial performance measurable in man. As detailed below, there are strong theoretical objections to its use as such. So far as factors influencing myocardial effort are concerned, ventricular end-diastolic pressure is a highly questionable index of end-diastolic volume. Attempts have been made to determine end-diastolic volume in man through the determination of residual volume by radiologic[40] or dye-dilution technics[41] (end-diastolic volume = residual volume + stroke volume), but these are difficult to apply and again would yield average values. The clinical observation that the normal human heart decreases in size radiologically upon change from supine to erect position, and at the commencement of physical exercise,[40] casts doubt on end-diastolic volume as the only, or even the most important, influence on myocardial effort.

With reference to the third point, measurements of cardiac oxygen consumption in man have been based on measurements of flow in the coronary sinus and its oxygen content.[42] However, the coronary sinus flow is *not* a certain measure of total coronary flow,[43, 44] nor does it necessarily indicate the mural flow in the left ventricle or any *fixed* portion of it in comparisons of a group of individuals.[45] In fact, recently the septal branch of the left descending coronary artery in the dog has been shown to drain principally via Thebesian channels.[46] Even in the same person, the drainage area of the coronary sinus may shift when the state of the individual is altered by drug or other procedure.[47] There is sufficient uncertainty, therefore, in this method to lead one to demand qualified evaluation of the data obtained when it is at variance with animal studies in which coronary flow measurements are more precise. This is further necessitated by the well-known fact that the coronary sinus blood does not represent an exact nor constant index of total coronary venous blood oxygen (or substrate) content.[48]

The data based on the coronary sinus method are, however, the best so far available in man. These indicate a correlation between external work of the heart and myocardial oxygen consumption.[49] It is also reported that the myocardial oxygen consumption of the area drained by the coronary sinus is normal in the presence of congestive heart failure.[50] Also, it rises on exercise as in the normal,[49] and is unaffected by digitalis.[50] The increase in myocardial oxygen consumption in the normal individual on exercise has been attributed to adjustments according to Starling's law.[49] This is open to question because, among other reasons, no measurements of end-diastolic volume were made. But more significant reasons for doubt are the newer con-

cepts of the performance of the heart that have recently arisen as a result of animal studies. They have been summarized elsewhere[6-9] and are discussed below as they relate to the development of a basic understanding of heart failure.

Mechanisms Involved in Experimental Cardiac Failure

Steps Involved in Muscle Contraction

Obviously congestive heart failure as defined must ultimately be referred to incompetence of the cardiac muscle, either as a primary event or secondary to an excessive load. We are concerned with the fundamental nature of the myocardial incompetence. Since energy is necessary for this performance of work, cardiac muscle energetics (metabolic sources of energy for myocardial contraction and its conversion to mechanical energy) is a good starting point for a systematic discussion of this matter. The terminology of Wollenberger is useful in this connection.[51] Energy *liberation* is defined as the process concerned with the *supply* of energy and includes both the enzymatic oxidation of substrates, such as glucose, lactate, and the coupled transfer of energy derived from oxidative processes to the so-called high-energy compounds such as adenosinetriphosphate, adenosinediphosphate, creatine phosphate—the process of oxidative phosphorylation. Energy *utilization*, on the other hand, is defined as the process concerned with the expenditure of the liberated and stored energy in the development of contractile tension and heat. In the strict sense, therefore, energy utilization is chemical-mechanical coupling—the link between energy liberation and its utilization as contractile tension. This subject has been recently reviewed by Hajdu and Leonard.[52]

Contractile tension in turn, once produced, is manifest *only* as muscle tension and heat, no external work being accomplished. Even in expresses it into the arteries. The amount of this conversion of tension to work depends on existing conditions, particularly on the amount and nature of the load on the heart.[8, 53] When the load is too great, or if other conditions prevent muscle shortening, energy utilization is manifest *only* as muscle tension and heat, no external work being accomplished. Even in this (isometric or, more accurately, isovolumic) type of contraction, however, shortening of the contractile elements of the heart muscle fiber still takes place, but, since the volume of the heart is not reduced the only result of this shortening is the rearrangement of the shape of the ventricle and a stretching of the elastic elements within the heart wall, which are in series with the contractile elements.

Possible Defects in Energy Transformation Which Lead to Heart Failure

On the basis of the foregoing considerations, heart muscle failure could, at least theoretically, result from (1) partial failure in energy liberation, either at the oxidative level or the chemical energy transfer level, or both; (2) inefficiency of energy utilization in the development of tension; or (3) inefficient conversion of contractile tension into external work. In the last 2 circumstances, an inordinate expenditure of energy would be necessary in order to maintain the normal capacity to do "external" work.

Impairment of Oxygen Use as a Cause of Heart Failure

Studies of oxygen usage, and of most of the common carbohydrate, lipid and amino acid substrates have been made in the normal and failing heart.[54] For the most part, these studies relied on coronary arteriovenous differences and simultaneous determinations of coronary flow correlated with parameters of cardiac effort. Since the substrates studied may be transmuted, stored, or oxidized and since their complete oxidation may require amounts of oxygen different from that consumed in terms of actual measurement,[55] such data would not appear to give a true picture of the rate of substrate utilization within the heart muscle. Oxygen usage, on the other hand, serves as a much better index of the over-all rate of oxidative metabolism. Since oxygen cannot be stored in significant amounts in the heart muscle, its disappearance rate

would seem a reliable index of its utilization. Because anaerobic energy-yielding reactions are relatively less important in comparison with the high yield of cardiac aerobic reactions, it is generally held that cardiac oxygen usage is a good index of the total amount of energy furnished for contraction and maintenance. This is borne out by the good correlation between indices relating cardiac effort to oxygen usage.

Comparison of the normal and failing heart reveals little difference in the rate of cardiac oxygen usage.[54] Thus, one is tempted to conclude that energy liberation, including transfer of oxidative energy in a form useful to the contraction process, is normal in heart failure. This appears to be substantiated by the lack of difference in the levels of the various high-energy phosphorus compounds or energy-storage substances between the normal and failing heart.[56]

Attempts to gain insight into the mechanism of *chemical-mechanical coupling* have been beset by major difficulties. Chief among these is the disparity between the findings in muscle models and in intact muscle.[57] Studies of muscle models have shown a utilization of adenosinetriphosphate during contraction and revealed the relationship of myosin as an adenosinetriphosphatase. Intact muscle, on the other hand, shows no discernible decrease in adenosinetriphosphate in a single twitch[58, 59] and there is no apparent difference in turnover rate of adenosinetriphosphate between contracting and resting muscle. Also, wide divergencies can be demonstrated when the rate of hydrolysis of adenosinetriphosphate is related to contraction in muscle preparations.[60] Therefore, it is hazardous in our present state of knowledge to speculate concerning the role of chemical-mechanical coupling in heart failure. However, emerging considerations regarding these mechanisms provide attractive pathways for future exploration of cause and effect relationships in cardiac failure.

Apart from the possibility of a defect in energy liberation, the integrity of the contractile protein (actinomyosin) comes into question in failure of the heart muscle. It is conceivable that acute or chronic failure might alter the character of such proteins and affect muscle response even in the presence of an adequate energy supply and its utilization up to this point. Indeed, two lines of investigation suggest that this is more than a possibility. Olson and Piatnek[61] found molecular weight changes in cardiac myosin after experimentally induced failure, and Benson et al.[62] noted a decrease in the tension response of glycerol-extracted myocardial fibers from failing hearts. However, the possibility that changes in elasticity could explain these results was not excluded in Benson's experiments.

While evidence to the contrary seems virtually complete, the possibility still exists that heart failure, at least under some circumstances, may be caused primarily by a defect in energy liberation that is not revealed by measurements of oxygen consumption and concentration of high-energy compounds.* In myocardial infarction, in which viable muscle is destroyed, there can be no doubt that heart muscle failure is due to loss of liberated energy, and a similar state may be more subtly induced in other disease states of the muscle (as in group 3 above). In cases such as these, the evidence of a deficit in energy liberation will be mirrored in a diminished cardiac effort. As recovery occurs, or compensatory

*One other concept should be mentioned in this connection. The heart in situ, as distinct from the isolated heart or that of the heart-lung preparation, may take up substrate from the blood as an energy source and pass incompletely degraded products back into the blood for oxidation in *other* organs. While this process of ebb and flow of substrate and degraded material must be small normally, the possibility exists that it may be significantly augmented in myocardial failure, thereby making the oxygen consumption of the heart a less perfect index of its energy liberation. For example, the cycle of blood glucose going to the heart and myocardial lactic acid passing back to the blood may be augmented in heart failure. This is an action which spares the heart, while yielding energy for it. The above must be considered only as a theoretical possibility.

mechanisms, e.g., hypertrophy of surrounding muscle, come into play, energy liberation, as well as heart function, will tend to return to normal.

Experimental studies by and large however, have led most reviewers to conclude that it is the process of energy utilization that is abnormal in heart failure. Until clean experimental evidence to the contrary is forthcoming, we cannot favor impairment of energy liberation as the ordinary mode of heart muscle failure. This conclusion appears to be supported by the fact that the external mechanical efficiency of the heart, the ratio of external work done to oxygen used, is decreased in heart failure.[54] Furthermore, it has been shown that measures taken to reverse failure also serve to restore toward normal this index of efficiency, both in the animal and clinically.[63] Unfortunately, this argument based on changes in external mechanical efficiency may be spurious, since the reduction in cardiac output and increase in heart rate that accompany heart failure would lead to a decrease in external mechanical efficiency even in the nonfailing heart.[4, 48] Thus, it may turn out that the reduction of efficiency is a secondary phenomenon accompanying changes in cardiac output and heart rate rather than a primary feature of heart failure. This matter cannot be regarded as settled.

Impairment of Chemical Energy Utilization for External Work as a Cause of Heart Failure

External work—used in the calculation of external mechanical efficiency—really does *not* exemplify the conversion of chemical to mechanical energy appearing as muscle tension.[53] In our view, the ideal index to myocardial effort would be the accurate determination of muscle tension of the ventricles, actual external work being incidental.

Some insight into the mechanism defect in heart failure may be revealed by a consideration of the development of tension in contracting heart muscle. The earliest studies of cardiac muscle were concerned with finding analogies between skeletal and cardiac muscle activity. O. Frank constructed idealized curves based on pressure-volume changes in the cardiac cycle and explained them on the basis of length-tension changes seen in skeletal muscle.[65] Characteristic curves relating pressure to volume were constructed for the heart in diastole and in systole, in both isometric and isotonic contraction. The actual pressure-volume changes occurring during a cardiac cycle were then superimposed upon this, to represent the actual expenditure of energy appearing as heart work. Later, Starling and his associates elaborated the general principles governing control of energy expenditure using the mammalian heart-lung preparation.[66] They extended Frank's observations by relating ventricular end-diastolic volume (i.e., the length of the muscle fiber) to the energy set free in the following systole.

In our own previous studies, the pressure-volume relationships that Frank had demonstrated and Starling had applied to the mammalian heart were used to define the viscous-elastic properties of the fully relaxed and fully contracted heart.[67] The curves so derived indicate respectively the *diastolic* and *systolic* tone of the heart. Diastolic tone can affect the end-diastolic volume and systolic tone helps to determine the systolic residue of the heart.

Further studies by Starling and others were based primarily on measurable hemodynamic variables. Exhaustive investigations were made of the effects of altering vascular resistance, venous return, and heart rate upon end-diastolic volume, end-diastolic pressure, and the extent of contraction.[68, 69] The preoccupation of these investigations with hemodynamic studies of this type led to neglect of the concept of tension. On the other hand, Wiggers and Katz,[70] in 1928, analyzed the intraventricular pressure curve and suggested that the area beneath the isometric portions of the curve and that part during ejection above arterial diastolic pressure should be taken to represent the "static effort," while that beneath the arterial diastolic pressure during the ejection portion of the curve should be considered as an index of "dynamic effort."

This distinction served to emphasize the large differences in tension expenditure associated with different aspects of muscle contraction during the cardiac cycle. These concepts of the character of the heart's effort were interpreted in terms of time-tension relationships found in skeletal muscle, in which a correlation between oxygen consumption and the duration of tension development had been demonstrated.[71]

Understanding of functional relationships has been materially advanced by morphologic considerations. Anatomic studies reveal that the majority of the myocardial fibers have both their origin and insertion on the valve rings, while a few are attached to the chordae tendineae or follow a circumferential path around the ventricles.[72] These facts added to the known physical relationships governing pressure and tension in a hollow viscus led to the realization that, other things being equal, a ventricle that is initially filled with a larger blood volume will require augmented contractile tension in elaborating the pressure necessary to open the semilunar valves and to maintain it above the arterial diastolic level. The *extent of shortening* thereafter and the relation of ejected volume to end-diastolic volume will determine the direction and rate of tension change associated with ejection.

Burch et al.,[73] in 1952, presented an extended theoretical analysis of these factors, with special reference to the consequence of cardiac dilatation such as is seen in heart failure. It was shown that contractile tension usually decreases in the normal heart during ejection because of the rapid decrease in internal surface area as the heart volume declines, and despite the continuing increase in pressure from the diastolic level to the systolic peak. However, when the heart is dilated, as in failure, ejection of the usual stroke volume is associated with relatively little shortening. Since the decrease in internal surface area is proportionately less, an *increase* in contractile tension may be required under these circumstances in order to raise blood pressure to the same systolic peak.

Another aspect of this same question has come under investigation in our laboratory[74] and that of Sarnoff et al.[75] In these studies, indices of tension were sought in relation to the oxygen cost in the intact heart. Evaluation of blood pressure, heart rate, and cardiac output showed that the first 2 were more closely related to oxygen requirements than the last. Thus, for any given heart size, blood pressure may be taken as a direct function of contractile tension per beat, and heart rate as a measure of the number of times tension is created. Together they serve admirably as an index to total tension developed over any period of time. The studies demonstrated directly that minute cardiac output, which receives so much attention in the calculation of external work and efficiency, is of minor importance as a measure of cardiac effort, whereas heart rate, which is usually ignored in these calculations, is of great importance.

Recently, we approached the problem of tension conversion to external work and the energy cost of tension development directly by measuring the oxygen cost of left ventricular tension in the absence of external work.[76] A fluid-filled balloon placed in the otherwise empty ventricle permitted the calculation of tension per beat exerted on the balloon along with the concomitant oxygen cost. The results indicated that oxygen cost is directly related to energy expenditure as tension per beat. The further conversion of the developed tension as external work is a secondary, far less significant factor that is related to the mechanical advantages or disadvantages dictated by the range of size and shape of the heart during its cycle.

It would seem logical to conclude from the above considerations that heart failure does not appear to be related to defects in energy utilization for tension development. Rather, it would seem that muscle tension in heart failure is not as productive of external work as in the normal heart. This relative ineffectiveness of muscle tension appears to depend on changes in heart size and shape with heart failure. Rushmer[77] in his elegant studies of

size changes in the intact unanesthetized animal has emphasized the range of dimensional changes in various diameters of the nonfailing heart. Further studies are needed along these lines, in which attention should be paid to the role of dilatation in the failing heart, and to its detrimental effect on the utilization of tension as external work. Perhaps it will turn out that this relationship fixes the limit of dilatation as a compensatory mechanism.

While it appears that the dilated failing heart requires considerably more contractile tension to meet the needs of a given load, no indication has been given as to how this dilatation comes about. It was evident in the "heart-lung period" that important differences could be discerned in the response to load between a fresh and a "tired" heart-lung preparation, as well as before and after treatment with insulin and glucose.[78] Primarily, these differences consisted in alterations in responsiveness of the heart—a greater output or an increased pressure being noted in the fresh heart or the one treated with insulin and glucose *independent* of any consistent increase in end-diastolic volume. These facts indicate that other mechanisms of cardiac control exist even in the heart-lung preparation in which the natural neural and humoral influences on the heart muscle are absent. On the other hand, as depletion gradually progresses, the heart in the heart-lung preparation still responded with augmented effort to an increase in load, this adjustment now being *dependent* primarily on the increase in end-diastolic volume. This last mechanism can therefore be considered to be the *basic* primitive adjustment upon which other mechanisms of finer adjustment are superimposed.

The failing heart during this early period of investigation was considered as merely an enlarged version of the normal heart. Enlargement in turn was considered as due in part to an increased filling pressure gradient and in part to a decrease in diastolic tone. The ability of such a heart to meet the demands for flow in the body was viewed as depending on whether or not it had reached the maximum size beyond which output would decline.

Newer information, based on a more intact nondeteriorating preparation subject to the usual neural and humoral stimuli, makes possible a better comparison between normal and failing hearts in terms of their responsiveness to various hemodynamic situations.

The distinctive characteristics of such a preparation may be briefly summarized:

1. The normal heart does not usually empty with each stroke, in fact as much as 50 per cent of the end-diastolic volume remains as end-systolic residue.[79]

2. The normal heart, at rest, has a characteristic size in relation to body size and weight for each species.[80]

3. The normal heart generally has a greater volume in the supine than in the erect position,[64] and has a characteristic relation of number of beats per minute to stroke volume (such that the rate is greater for smaller outputs).[81]

4. In the face of a growing load, the normal heart may first decrease in size—meeting the increased output demands with greater stroke volume through mobilization of end-systolic residue. Further load may then lead to an increase in heart rate. Only when the load is increased still further does the heart increase in size and bring end-diastolic volume into play.

5. Wild animals of a given species have larger hearts in relation to their body size and weight than tame ones. This relation has also been found in trained athletes as contrasted with untrained individuals.[80] In athletes, there appear to be a greater end-systolic residue and a characteristically slower heart rate in relation to a given work-load. Further, in athletes, an increase in load tends to cause a greater stroke volume with minimal increases in heart rate as contrasted with the untrained person in whom heart rate acceleration is marked and early.

The failing heart appears to resemble the trained heart in the sense that both are

enlarged and both appear to have augmented end-systolic residues. Superficially the failing heart would seem to have the same potential advantages as does the trained heart, i.e., a lower heart rate for a given output and a greater reserve of mobilization. However, the epitome of heart failure seems to be the loss of these 2 advantages. Systolic residue does not appear to be available for the augmentation of stroke volume in meeting the challenge of an increased work load. Nor does end-diastolic volume appear to be so effective. Instead, tachycardia is the mechanism by which an attempt is made to increase minute-output. Because these advantages are lacking, the failing heart has been likened to the heart in the deteriorated heart-lung preparation, which also lacks these capacities.[82, 83] Like the latter, the failing heart needs a greater end-diastolic volume in order to increase output and overcome augmented systolic loads, rather than being able to draw upon end-systolic residue in the first instance and to react independently of end-diastolic volume in the second instance. Apparently this dependence of myocardial effort on end-diastolic volume represents a primitive regulation, or the last resort of a failing heart.

Contractility and Distensibility of the Heart in Failure

The capacity to mobilize end-systolic volume and in general to react independently of end-diastolic volume is attributed to that characteristic of muscle known as *contractility*. Contractility has so far lacked a sufficiently precise definition. In the cardiovascular literature one finds it referred to several phenomena relating to the responsiveness of the entire heart or heart muscle strips. A positive inotropic response usually indicates augmented force of contraction after drug or hormonal exhibition or neural stimulation. Treppe (the staircase effect)[84] encompasses augmented contraction following (1) a period of rest, (2) post-extrasystolic potentiation, and (3) increased frequency of stimulation. Catacholamine exhibition[85] and changes in the ionic milieu, notably a decrease in potassium ion and an increase in calcium ion, also augment contractility.[86]

It appears at present that contractility is, in its broad sense, a manifestation of responsiveness to many different stimuli, some mediated via the autonomic nervous system and others via humoral pathways. Rushmer's[77] efforts to elucidate this responsiveness in the normal, unanesthetized animal must be singled out as noteworthy and revolutionary.

The most important characteristic of contractility for the purpose of this discussion appears to be an ability to vary the extent of shortening for a given end-diastolic volume. More marked shortening in these circumstances has the effect of mobilizing the systolic residue of the heart. Thus, it would seem that the failing heart—dependent on a minimal mode of responsiveness—dilated and unable to mobilize the large systolic residue, lacks or is relatively deficient in that property of muscle considered as contractility.

Clear experimental evidence relating to differences in contractility, or similar properties (otherwise designated), between the failing and normal heart is not yet available. Perhaps restating these concepts will stimulate much-needed research in this direction.

Several recent studies that have provided further insight into the intrinsic nature of contractility are reviewed here on the basis of their potential significance in the understanding of changes in failing cardiac muscle. Abbott and Mommaerts,[87] in a study of the inotropic mechanism of isolated papillary muscle, considered the change in muscle response to be an alteration of the force-velocity relationship of the contracting mechanism. Hill[88] had demonstrated that the velocity of contraction is empirically related to the load that could be defined by a specific characteristic curve. Thus, knowing the work-load and the conditions of contraction, one can calculate the velocity. Force-velocity curves were found not to be superimposable after inotropic augmentation, implying that the beat of papillary muscle became both faster

and stronger on stimulation. Thus, a greater beat frequency shifted the optimal efficiency of the muscle so as to cause a greater velocity of shortening. To quote: "The heart adjusts its internal characteristics so that at greater speeds of action it is optimally efficient at greater speeds of shortening."[87]

Alternatively, a change in contractility may depend on an alteration of the "active state." This alludes to a muscle change that precedes and coexists with the actual contraction, and without which a contractile response is impossible. The "active state" is presumed to be a state of readiness to contract that must occur after stimulation and before the manifest response. The duration of the active state is appreciably shorter than the mechanical response. It has been shown that an increased duration of the active state leads to a higher and more sustained twitch tension. Abbott and Mommaerts found that the duration of the active state was unchanged or even decreased when the intensity of contraction was increased.[87] Trendelenburg and Lüllman[89] also failed to find any apparent change in the duration of the active state associated with increased stimulation frequency or with alteration of the length-tension relationship. Niedergerke,[86] however, found that a milieu rich in calcium ion did increase the duration of the active state of cardiac muscle.

The special significance of the active state for the intensity of the ensuing contraction provides an attractive speculation on one possible advantage of cardiac dilatation. Before stimulated muscle begins to shorten, the contracting elements take up the slack of the elastic components in series with them. Prior stretch, which would passively remove this slack or even stretch the elastic elements, would permit the fuller use of the active state for the actual act of shortening. Thus, there is an advantage to a certain degree of dilatation in that the full potential of the active state for shortening can be utilized. However, such an advantage may only be temporary. Chronically stretched fibers may lose their resting tension and thereby the mechanical advantage of the stretch, as a result of plastic elongation and "creep." These are essentially hysteresis phenomena and occur after prolonged extension under load, so that the initial length is not attained upon release. Such changes in physical properties may become irreversible in the dilatation of the failing heart.[90]

Contractility is only one inherent property of the heart. Distensibility is another. While contractility is associated with the extent, velocity, and force of *shortening,* distensibility is associated with the extent, and rate of *relaxation* of a ventricle. The extent of relaxation has been appreciated for some time and labeled as the diastolic tone of the heart.[67] The course of relaxation is important in setting the mode of contraction of the heart. The velocity and duration of relaxation appear to have special significance in terms of the rate of filling of the heart when filling time is limited as in tachycardia. The phase of active relaxation appears to be more closely related to the restitutive chemical processes that are required for sustained activity. Brewster et al.,[91] have shown that the enzymatic reactions that occur during relaxation have a large Q_{10}, and a large energy transfer, as would be expected in relation to chemical-mechanical coupling. Contraction, on the other hand, is associated with processes having a small Q_{10}, usually associated with ionic forces and insufficient to account for contraction energy expenditures. Further, it has been found that the metabolic rate in diastole is related to its duration.

Hill and Howarth[92] have presented evidence that the act of stretching a skeletal muscle fiber is associated with the addition of energy to the fiber. Active relaxation (in terms of energy exchange) and passive extension of the fibers by the inflowing blood thus would appear to be related. Part of the chemical energy potential may be lost when forces in the muscle resist extension through incomplete relaxation. Buckley and her associates[93, 94] have made an extensive study of the relaxation process in the mammalian ventricle, par-

icularly with reference to impedance and ompliance during filling. These terms are ntonyms and relate to the resistance to filling nd the extent to which the ventricle walls xpand upon being filled. The amount of illing is related not only to the time available or filling but also to these concurrent changes n the physical properties of the muscle that esist or facilitate filling. These impedance hanges were related by Buckley et al., to hanges in its viscous-elastic properties—a relationship already noted previously by others in the consideration of the systolic and diastolic tone of the heart. Most recently, Buckley et al.[94] found that a decrease in compliance and an increase in impedance occur during acute heart failure in the dog, changes which were irreversible. This represents another dimension in physical properties, similar to those considered relative to the systolic phase of the cardiac cycle. They are likewise subject to change and may be involved in the process leading to or resulting from cardiac muscle failure in man.

Conclusions

From all of this it would seem that the phenomena of heart failure reside in the heart muscle and are involved in its size, shape, and the physical properties during relaxation and contraction that determine its distensibility and contractility. These last are set by the metabolism and chemical milieu of the cardiac muscle, and are primarily physical, chemical, and biophysical in character. They may be determined by anatomic and geometric alterations as well. At present, it would seem that the energetics of the heart in terms of energy release and of utilization of chemical energy for the development of muscle tension are less often involved in heart muscle failure, than is the conversion of tension to external work. This background has made the development of heart muscle failure easier to understand. It would be hazardous to say that the subject is settled, but it is safe to assume that the directions for further study have been established.

Our purpose has been to review the subject of hemodynamics in congestive heart failure as it stands today. The picture of course is still crude, but the outlines depicting the true nature of congestive heart failure are dimly discernible. Future work will doubtlessly bring it into sharper focus.

Conclusions in Interlingua

Le objectivo del presente articulo es revistar le hemodynamica de congestive disfallimento cardiac secundo le stato currente del recerca. Le autores insiste que le ver natura de congestive disfallimento cardiac ben que illo es certo non ancora clar, comencia al minus devenir recognoscibile in su contornos general. Investigationes futur va sin dubita succeder a focalisar lo plus nettemente.

Super le base del datos jam establite il pare que le phenomenos de disfallimento cardiac ha lor sito in le myocardio e es interessate in le dimensiones e le conformation de illo si ben que como in su proprietates physic de relaxation e de contraction le quales determina su distensibilitate e su contractilitate. Iste ultimes depende del metabolismo e del chimismo del myocardio e es primarimente de character physic, chimic, e biophysic. Illos etiam pote esser determinate per alterations anatomic e geometric. Al tempore presente il pare que le energetica del corde—i.e. le provision de energia e le utilisation de energia chimic in le disveloppamento de tension muscular—es interessate minus frequentemente in disfallimento myocardial que le conversion de tension in labor externe.

Iste constatationes forni un plus firme base pro le comprension del disveloppamento de disfallimento myocardial. Le autores assere que il esserea riscose mantener que le question es resolvite sed que il es permissibile insister que al minus le direction in que investigationes futur debe avantiar es clarmente establite.

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Metabolism of the Heart in Failure

By Wm. H. Danforth, M.D., F. B. Ballard, M.D., K. Kako, M.D., J. D. Choudhury, M.D., and R. J. Bing, M.D.

HEART failure may be considered from a variety of viewpoints and studied by diverse methods. Research into the clinical and hemodynamic aspects of congestive failure has uncovered much useful information; however, the basic question remains unanswered: What changes in the myocardium lead to deficient emptying of the heart and thence to heart failure? In recent years, modern technics have made possible direct study of the cardiac muscle in attempts to understand how it converts energy derived from substrates into useful work and to uncover derangements that may lead to insufficiency and failure of the heart. While this problem is far from solved, progress has been made and unresolved questions have been brought into sharper focus.

Normal Cardiac Metabolism

The heart extracts foodstuffs and oxygen from the coronary blood; energy must be released from the metabolism of foodstuffs and transferred to the effector structures, the contractile proteins of heart muscle. A schematic representation is found in figure 1 in which cardiac metabolism is arbitrarily divided into 3 phases: energy production, energy conservation, and energy utilization.[1] By introduction of a catheter into the coronary sinus, myocardial extraction of substrates and of oxygen may be measured in the intact animal or man without disruption of normal physiology.[2, 3] By determining the content of various foodstuffs or oxygen in simultaneously obtained arterial and coronary sinus blood samples and by measuring coronary flow,[4] the myocardial extraction and usage of these substances may be calculated. It is then possible to obtain the percentage of oxygen utilized in the metabolism of any individual substrate (the oxygen extraction ratio).[5] These studies have shown that the heart can extract glucose, pyruvate, lactate, fatty acids, amino acids, and ketones from the arterial blood. The actual myocardial extraction of carbohydrates varies within certain limits with the arterial concentration.[6, 7] Thus, in the postabsorptive state the oxygen extraction ratio of carbohydrates is high, illustrating that under these conditions these substances furnish the major portion of available energy of the heart; in the fasting state, however, utilization of fatty acids accounts for a major portion of the total usage of myocardial oxygen, with an oxygen extraction ratio of 67 per cent as compared to 35 per cent for carbohydrates[8] (table 1). After ingestion of a fat emulsion the oxygen extraction ratio for total fatty acids rises to 132 per cent, suggesting storage or incomplete metabolism of fats.

Recent studies conducted in this laboratory and elsewhere have further defined the myocardial utilization of fatty acids. Gordon and Cherkes have shown that the nonesterified fatty acid fraction of plasma (NEFA) is the lipid fraction primarily concerned with the transport of fats to tissue.[9] These authors demonstrated that NEFAs were extracted by the heart. However, Fredrickson has shown that a large fraction of the chylomicron triglyceride appears to be utilized without first appearing in the plasma NEFA fraction.[10] In this laboratory it has been found that less than half of the fatty acids consumed by the

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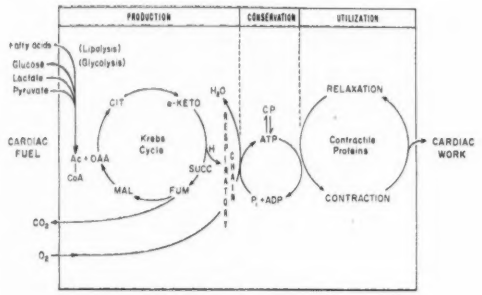

Figure 1

Schematic representation of myocardial metabolism (modified from Olson[1]).

myocardium are derived from the NEFA fraction.[11] These data strongly suggest direct myocardial utilization of the esterified fraction. As opposed to carbohydrates, the myocardial usage of NEFA is not directly correlated with arterial concentration. During alimentary hyperlipemia, heparin induces a moderate rise in the arterial level of NEFAs, but only an insignificant increase in their myocardial usage[11] (fig. 2). On the other hand, myocardial usage of NEFA appears to be related to the nutritional state of the moment. When carbohydrate substances are available, they appear to be used preferentially, while NEFA usage declines. In the presence of readily available carbohydrates, both the arterial NEFA concentration and the myocardial usage of NEFA drop to low levels.[12]

At cardiac catheterization, the iodine number of the total fatty acid fraction of arterial and coronary sinus blood has been determined in this laboratory. The iodine numbers of the coronary sinus samples are consistently higher than those of the arterial samples, suggesting that the heart utilizes preferentially saturated fatty acids.[11]

Under normal conditions, the heart extracts most of the available oxygen from the coronary blood.[4] Increased demands for oxygen must therefore be met almost entirely by increased coronary blood flow.[13] The dependence upon rapid changes in coronary blood flow is evident when one realizes that the heart must be able to meet sudden demands for increased output without incurring an oxygen debt.

Table 1

Relative Contribution of Carbohydrates and Noncarbohydrates to Total Myocardial Oxygen Usage in the Postabsorptive State

Carbohydrate, %		Noncarbohydrate, %	
Glucose	17.90	Fatty acids	67.0
Pyruvate	0.54	Amino acids	5.6
Lactate	16.46	Ketones	4.3
TOTAL	34.90%	TOTAL	76.9%

Energy is obtained from the available foodstuffs by stepwise degradation taking place primarily in the tricarboxylic acid cycle. The release of energy is almost entirely aerobic and mediated by the respiratory enzymes.[14] The energy produced by substrate oxidation must be harnessed; to accomplish this, the energy release is coupled with the formation of high-energy phosphate bonds.[15] The heart contains largely adenosine triphosphate (ATP) and smaller amounts of creatine phosphate, which probably functions as a high-energy phosphate reservoir. On the average, about 3 molecules of high-energy phosphate are produced for each atom of oxygen utilized.[16] The energy is then held as high-energy phosphate until employed by the contractile proteins. Since it has been found that the arrested heart requires about 20 to 35 per cent as much oxygen as does the quietly beating heart,[17] one may calculate that 65 to 80 per cent of the phosphate energy bond is utilized for muscular contraction. If allowances are made for the energy requirements of the nonbeating heart, the left ventricle converts about 38 per cent of the available oxidative energy into useful work.[18]

Myocardial energy then is made available by substrate oxidation and is captured and conserved as high-energy phosphate, but the burden of the actual work of the heart falls to the contractile proteins, actin and myosin.[19]

The discovery that the muscle proteins, actin and myosin, combine to form actomyosin complex, the contractile protein in muscle,

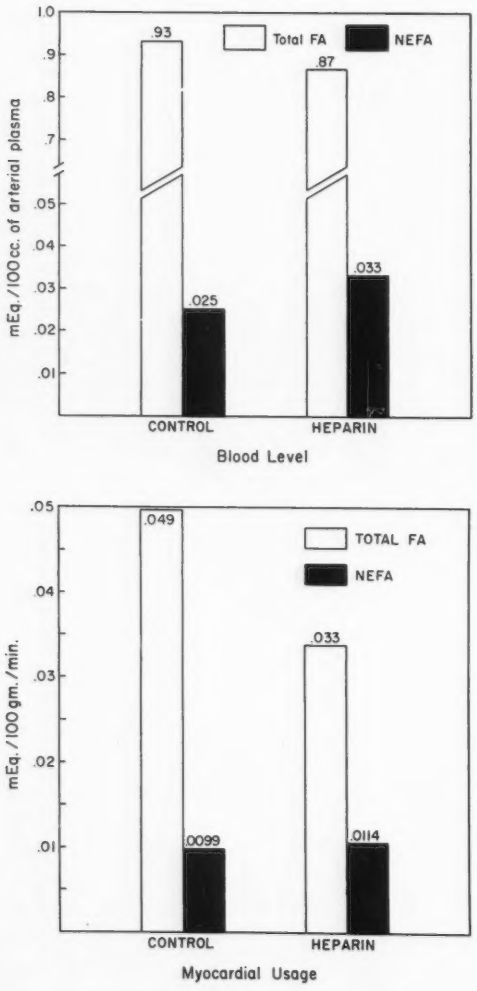

Figure 2

Top. *The effect of heparin on the average arterial plasma concentrations of total fatty acids (total FA) and nonesterified fatty acids (NEFA) in 8 dogs.* Bottom. *Simultaneous myocardial usage of total FA and NEFA in the same 8 dogs. Despite a rise in the arterial NEFA levels there is only minimal increase in the NEFA utilization.*

has shed much light on the nature of the alterations occurring in contracting muscle at the molecular level.[19] The muscle protein myosin itself has ATPase activity, which is inhibited by magnesium and activated by calcium.[20] Actually, myosin itself can be split by proteolytic digestion into 2 components, only one of which is endowed with adenosinetriphosphatase activity. This adenosinetriphosphatase activity plays an important role in muscular contractions by breaking down ATP, a high-energy phosphate compound, into adenosine diphosphate (ADP) and inorganic phosphate, thus making the energy available for muscular contraction. Actin is obtained from the muscle residue from which myosin and all other soluble proteins have been extracted; a globular or G form is contained in aqueous extracts, but salts change this into the fibrous or F actin. Here, too, ATP is important, since it is involved in the polymerization of actin and may be an important part of the actin molecule. One of the most striking properties of F actin is its ability to form a complex with myosin, leading to the formation of actomyosin;[19] this compound has high viscosity and possesses a considerable degree of adenosinetriphosphatase activity in the presence of magnesium. When ATP is added to actomyosin, striking physical changes, such as a drop in viscosity, occur. Although actual mechanisms remain unknown,[21] it is probable that the interactions among actin, myosin, actomyosin, ATP, and the various ions are responsible for the events taking place during contractions of skeletal and heart muscle.

It is of particular interest to those concerned with the molecular basis of heart disease, that these contractile proteins of the heart can be studied in systems that stand halfway between the whole muscle and protein enzyme preparations. There exist several of these models. In one of these, ions including potassium and sodium as well as ATP have been removed by prolonged extraction of the muscle strips in water and glycerol. These glycerinated fiber models contract upon addition of ATP.[19] Another method for reconstruction of a model of the contractile system consists in producing surface films of actomyosin solution that can be compressed into bands. With this method, one can record, without appreciable friction, shortening of the band at considerable magnification.[22]

Heart Failure

The dynamic manifestations of cardiac failure from any cause are similar. There are no reasons, however, for assuming that the underlying mechanisms of different types of failure are the same or even similar. For the purpose of this discussion, failure of the heart is divided into 3 groups. Under group I, heart failure associated with prolonged overload of the heart muscle fibers such as occurs with hypertension, valvular heart disease, and arteriosclerotic heart disease is considered. In support of this particular grouping is the fact that the myocardial metabolism of the members of this group appears to be identical.[23] Group II consists of all the types of heart failure in which a metabolic factor may be involved. Each entity in this group is considered separately without the implication that the underlying causes are similar. Lastly, group III consists of the failure of the isolated heart.

Group I

Chronic congestive heart failure such as occurs with hypertension, valvular heart disease, and arteriosclerotic heart disease is difficult to obtain experimentally. As a result, most of the data has been obtained in human beings. Studies have been published on the utilization of myocardial substrate in normal individuals, in patients with compensated heart disease, and in those with congestive failure. Myocardial uptake of glucose, pyruvate, fatty acids, and ketones was not altered by heart disease or by chronic congestive failure[22] (fig. 3). In addition to normal myocardial usage of substrates, patients with compensated or decompensated heart disease have normal coronary blood flow and normal myocardial oxygen usage per weight of heart muscle, despite increased diastolic heart size (fig. 4). Since the failing heart during exercise can increase its oxygen uptake, there appears to be no impediment to the delivery of oxygen to the myocardium.[24]

Digitalis preparations do not affect coronary blood flow or myocardial oxygen consumption significantly in the normal or failing

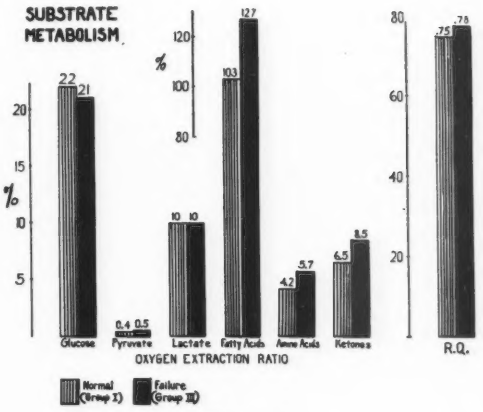

Figure 3

Relative contribution of the individual foodstuffs to oxidative metabolism of the normal and failing heart. It may be seen that the differences between the 2 groups are minimal. The respiratory quotients are essentially the same. (Republished by permission of the American Journal of Medicine.[23])

human heart.[25] There is no significant effect of lanatoside-C on utilization of myocardial substrate despite improvement of the work capacity of the failing heart.[26] Thus, myocardial substrate utilization, oxygen consumption, and coronary blood flow are not significantly affected in patients with congestive heart failure included in group I, nor is there any change as the heart failure recedes after digitalis. Essentially similar results have been found by other investigators.[27–29]

The normal utilization of substrates and oxygen by the failing heart suggests that the underlying defect may be located in energy conservation or utilization. A relative lack of high-energy phosphate due to rapid deterioration or inefficient formation from normal oxidation must still be considered.[30] Wollenberger demonstrated that heart failure could take place in the dog heart-lung preparation in the presence of normal or even elevated levels of high-energy phosphate.[31] This is in line with the report of Olson and Piatnek that levels of ATP and creatine phosphate are also normal in chronic and congestive heart failure in dogs with induced valvular disease.[32]

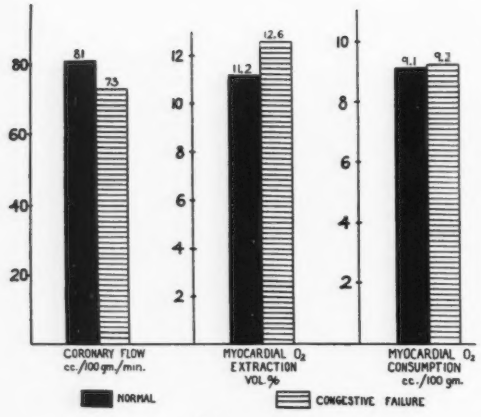

Figure 4

Myocardial oxygen consumption. In 22 patients with congestive failure the mean coronary flow was slightly lower than the average found in 16 normal patients. However, the coronary arteriovenous oxygen difference in the decompensated patients was sufficiently increased so that the oxygen consumed by equal weights of heart muscle was the same in both groups. (Republished by permission of the American Journal of Medicine.[23])

Furthermore, oxidative phosphorylation in mitochondria obtained from heart of guinea pigs in chronic congestive failure is normal.[33]

Therefore, by exclusion, the evidence points to the organs of energy utilization, the contractile proteins, as the site of the derangement in the myocardium of this group. Studies undertaken on actomyosin bands, although not yet conclusive, support this contention. Thus, it has been shown that the contractility of these bands from hearts of human subjects dying from congestive failure is impaired. Digoxin failed to correct this defect, but the combination of Digoxin and calcium chloride restored the normal contractility.[22] Benson has demonstrated that both the concentration and the viscosity of actomyosin are reduced in dogs with chronic heart failure secondary to surgically produced valvular disease.[34] Later he and his co-workers found impaired contractility of glycerol extracted muscle bundles from the chronically failing canine heart.[35] Physicochemical characterization of myosin by Olson and co-workers has given considerably higher estimates for molecular weights of myosin prepared from failing than from normal hearts; differences in molecular configuration of myosin were also described.[36, 37]

More information is still needed before the basic underlying defect in congestive heart failure is clearly delineated. However, certain tentative conclusions are warranted. For example, it is likely that alterations in the molecular structure of contractile proteins induced by chronic stretch of these fibers may lead to deficient contractility of the heart in congestive failure. In addition, in both heart failure as seen in this group and in failure of the heart in the heart-lung preparation, the myocardial oxygen consumption is normal or diminished. It is apparent from several studies that the oxidative functioning of heart muscle sarcosomes, like liver mitochondria, is under some sort of regulatory system. It has been mentioned in previous paragraphs that during muscle contraction and elongation ADP is formed from ATP. Thus, the main source of ADP in the muscle cell is the actomyosin system itself.[38] In addition, mitochondria are responsible for the formation of ATP. Changes in contractile proteins may result in diminished formation of ADP from ATP because of defective adenosinetriphosphatase activity. Lardy and Wellman have shown that ADP formation must occur in order to achieve oxidation of substrates.[39] Consequently, failure to increase oxygen utilization when the heart is dilated in failure may be related to lack of increased release of ADP by malfunction of contractile proteins. Studies concerned with the adenosinetriphosphatase activity of actomyosin prepared from human hearts would be of great theoretical and practical interest.

Group II

Anemia and Anoxia

As stated previously, this group includes heart failure in which a metabolic factor may be involved. Increased cardiac output and tachycardia are known to exist in this condition. Because of the decreased blood oxygen carrying capacity the myocardial oxygen ex-

fraction falls. However, the coronary blood flow rises markedly and the total myocardial oxygen consumption may be higher than in the normal person.[40] Experiments in the open-chest dog have shown similar results in coronary blood flow in response to anemia. When the hematocrit is reduced to levels of 24 to 31 per cent, there is depression of ventricular function curve.[41] This loss of the ability of the heart to increase its work occurs when the coronary bed is near maximum dilatation, suggesting that, despite coronary vasodilatation, delivery of oxygen to the myocardium is inadequate. The mechanism of rapid spontaneous failure of the heart in the heart-lung preparation under anoxic conditions is probably comparable to that described in anemia; it is likely that in both conditions failure is the result of inadequate energy production by the heart. Thus, Fawaz and associates have shown that under anoxic conditions, the creatine phosphate content of the isolated heart is reduced.[42] Experiments in this laboratory have furthermore demonstrated that during anoxia there is a rapid diminution of creatine phosphate, ATP, and glycogen, while the level of hexosemonophosphate increases.[43] These changes are compatible with rapidly progressing glycolysis, and suggest that under these conditions the enzyme phosphofructokinase may be the rate-limiting enzyme. Even brief anoxia, as present during angina pectoris, and localized anoxia during myocardial infarction lead to demonstrable glycolysis, as evidenced by increased lactate levels in coronary sinus blood.[44, 45]

Myocardial Failure in Hemorrhagic Shock and Myocardial Infarction

Myocardial anoxia is also responsible for myocardial failure observed under these circumstances. In hemorrhagic shock, the myocardial oxygen consumption is diminished during both the oligemic and the normovolemic phase and localized ischemia is present in coronary occlusion. In hemorrhagic shock, observations on the effective atrial pressure, ventricular volume changes, and intraventricular pressures have demonstrated that the deterioration of myocardial expulsive power contributes to progressive circulatory failure.[46] Circulatory failure even persists after restoration of normal blood volume, demonstrating the presence of an irreversible state (the normovolemic phase).[47] The diminution in coronary flow results in definite disturbances in general metabolism, in which the heart is also involved. There is evidence that generalized systemic glycolysis and concentrations of pyruvate in coronary venous blood are increased above those of arterial blood; the myocardial extraction and usage of glucose is also diminished.[47]

Myocardial infarction also leads to acute myocardial failure if the uninvolved portion of the myocardium fails to compensate for the loss of contractile power of the ischemic muscle. Under these circumstances, there is a decrease in stroke volume and a compensatory increase in peripheral resistance. Metabolic changes suggest that myocardial ischemia is accompanied by rapid glycolysis taking place in heart muscle. Pyruvate and lactate concentrations in coronary venous blood frequently exceed those in arterial blood. Myocardial glycolysis is also present in the arrested and fibrillating perfused heart. This disturbance in energy production may conceivably lead to diminished expulsive power of the heart and to progressive circulatory failure.[47]

Hyperthyroidism

Thyrotoxicosis is frequently associated with congestive heart failure but the failure may be reversed following adequate therapy. The increased total-body oxygen consumption, cardiac output, and heart rate are well recognized. However, increased cardiac load seems inadequate to account for the associated heart failure and metabolic factors have often been suggested. Early studies with coronary sinus catheterization suggested that the oxygen consumption of the heart in thyrotoxicosis was normal;[40] however, as more patients were studied, it became apparent that the heart of both thyrotoxic man and dog did partake in the general increase of body metabo-

lism,[48-50] although recent observations cast doubt on this supposition.[44] The coronary blood flow, the myocardial substrate utilization, and the oxygen consumption are all increased. Myocardial oxygen utilization returns to normal following remission of thyrotoxicosis.[48] Normal myocardial extractions of glucose, lactate, and pyruvate have been reported in thyrotoxic patients;[49] in hyperthyroid dogs these extractions were diminished.[50] Thyroid hormone results in "uncoupling" of oxidative phosphorylation, leading to inefficient energy conservation; under these conditions more oxidation of substrate is required to produce the same amount of high-energy phosphate. Heart mitochondria are particularly susceptible to this effect of the hormone.[51] Therefore, if this effect were present in vivo, one might expect high-energy phosphate compounds to be reduced in the myocardium in the presence of heart failure associated with thyrotoxicosis. Piatnek and Olson could not confirm this in thyrotoxic dogs;[32] however, the animals were apparently not in heart failure and consequently insufficient energy conservation still remains a possible cause of congestive heart failure seen in thyrotoxicosis.

Thiamine Deficiency

It is now known that thiamine pyrophosphate (cocarboxylase) catalyzes the reactions pyruvate to acetyl Co A, and α-ketoglutarate to succinate as well as the transketolase reaction. However, the relationship between these biochemical disturbances and the physiologic manifestations of the disease still remains obscure. The heart muscle like other tissue is unable to utilize lactate and pyruvate normally.[52] In dogs with thiamine deficiency at low rates of coronary blood flow the myocardial oxygen extraction is high; at larger flow the oxygen content of coronary sinus blood is elevated to a greater degree than expected, resulting in a marked diminution of myocardial oxygen extraction. This abnormal relationship between coronary blood flow and myocardial oxygen utilization suggests that deranged metabolism may result in insufficient energy production,[53] which could well account for the decreased ATP levels observed in the hearts of thiamine-deficient rats[54] and may also explain the heart failure seen in beriberi.

Group III

Spontaneous Failure of the Isolated Heart

Acute myocardial failure can be experimentally produced in the heart-lung preparation; heart failure usually occurs spontaneously 2 to 4 hours after the heart and lungs have been separated from the rest of the organism.[55] Many suggestions have been made to explain this specific failure of the isolated heart, but there have been no definite conclusions. Heart failure in the isolated heart has some mechanical features in common with chronic heart failure as it occurs in patients with congestive heart failure. In both instances there is an increase in the end-diastolic pressure and diminution of the stroke volume.[56] However, there are notable differences. In the first place, the element of hypertrophy is missing. Secondly, the oxygen consumption of the isolated heart is diminished, while that of the failing heart in situ remains normal.[57] Thus, in the acutely failing heart in vitro both cardiac work and oxygen consumption are diminished, while in clinical congestive heart failure the myocardial oxygen consumption remains normal despite the decrease in work.[23]

What is the cause for the spontaneous heart failure occurring in the heart-lung preparation? Several possibilities exist. The first is that it is the result of alterations of the contractile proteins of the heart. Studies have been performed in which the shortening of actomyosin bands prepared from spontaneously failing hearts in the heart-lung preparation were recorded; the contractility of actomyosin prepared from hearts failing in these preparations remained unimpaired.[22, 57]

Therefore, it is likely that the mechanism of spontaneous failure does not lie in organs of energy utilization. Since the extraction of substrates by the isolated failing heart remains normal, one must look for disturbances not connected with the utilization of sub-

trates. A clue to the possible mechanism of spontaneous failure may be sought in the work of Rein, who showed that the inclusion of liver and spleen in the perfusion circuit of a heart-lung preparation increased myocardial efficiency.[58] It is not clear from his studies whether or not the spleen actually releases a substance that is transformed by the liver into the active principle. However, it could be established here, in confirmation of the work of others, that the inclusion of both liver or spleen increases the myocardial efficiency slightly, primarily by a diminution in the oxygen consumption of the heart. Cardiac work is not altered.[57]

The question arose as to the nature of the active principle or principles in these organs. The likelihood existed that spontaneous myocardial failure in the heart-lung preparation results from lack of catecholamines in either heart muscle or the perfusion fluid; the rise in myocardial efficiency resulting from the inclusion of liver and spleen in the perfusion circuit might then be the consequence of partial restoration of the depleted supply of these substances. It is known that the spleen contains large amounts of norepinephrine because of its abundant supply of sympathetic nerve endings.[59] There are also considerable amounts of norepinephrine present in heart, muscle, ciliary bodies, liver, and to a lesser extent, the lung.[60] The concentration of norepinephrine in these organs appears to be related to their adrenergic nerve supply.[61]

In order to prove that lack of norepinephrine is responsible for the spontaneous failure of the isolated heart and that addition of this catecholamine by the spleen or the liver counteracts this condition, it is necessary to answer the questions whether norepinephrine reproduces the effects of liver and spleen on the isolated heart and whether it raises cardiac efficiency by lowering myocardial oxygen consumption without raising cardiac work. In addition, information is essential on the catecholamine content of the spontaneously failing heart or its perfusion fluid. It is known that the infusion of relatively large amounts

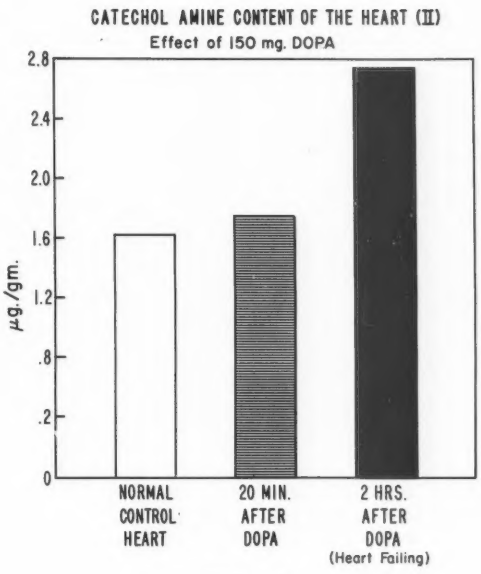

Figure 5

Catecholamine content of the dog heart. Twenty minutes after addition of dihydroxyphenylalanine (Dopa) to the heart-lung preparation, the catecholamine content is normal. At this time the efficiency of the heart had been improved. Two hours later the heart was failing despite high myocardial concentration of catecholamines.

of catecholamines diminishes the efficiency of the isolated heart;[62] however, the situation is quite different when very small amounts of norepinephrine or dopamine are used in these preparations. This results in an increase in the myocardial efficiency because the oxygen consumption of the heart diminishes while cardiac work is not altered.[57, 63]

Is the heart muscle or the perfusion fluid in the heart-lung preparation depleted of norepinephrine? It has been previously mentioned that the heart contains appreciable quantities of norepinephrine. Experiments were performed in which the norepinephrine content of hearts rapidly removed from the animal was compared to that of the heart maintained in the heart-lung preparation for at least 1 hour. There is no appreciable difference between the 2 preparations.[57] This finding illustrates that the presence of nor-

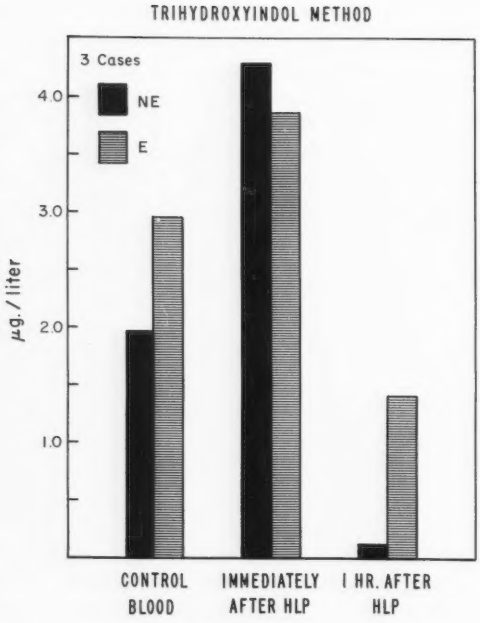

Figure 6

Norepinephrine (NE) and epinephrine (E) concentration in blood of normal dog immediately after completion of a heart-lung preparation (HLP) and 1 hour later. Values for NE and E were determined by the trihydroxyindol method.[64]

epinephrine in the isolated heart does not prevent the development of spontaneous heart failure. This becomes particularly clear when dihydroxyphenylalanine (Dopa) is added to the perfusion fluid. This procedure is known to increase the concentration of norepinephrine in heart muscle.[64] Even after the positive inotropic effect of the conversion products of dopa (dopamine and norepinephrine) has disappeared and the performance curve of the heart again shows the presence of failure, the concentration of norepinephrine in heart muscle remains elevated[57] (fig. 5). Apparently stored norepinephrine does not affect myocardial contractility; similar to acetylcholine, it may be inactivated by special binding to proteins and only suprathreshold stimulation, nicotine, or reserpine can establish the link between the amine and the effector organ.[65–67]

Studies on the catecholamine content of the perfusion fluid of the heart-lung preparation suggest a significant diminution of these substances (fig. 6). This information is based on the determination of catecholamines with the potassium ferricyanide method of Euler which determines only compounds carrying the amide group, on which pharmacologic activity depends.[64] It is also possible that lack of cholinergic substances is a contributing factor.

Conclusion

Investigations of the 3 phases of cardiac metabolism—energy production, energy conservation and energy utilization—have shown marked differences in the underlying mechanisms of heart failure. Thus, in failure with prolonged overload of the myocardium as occurs with hypertension, valvular heart disease, and arteriosclerotic heart disease (group I), an abnormality of energy utilization seems most likely. In the diverse situations with heart failure considered under group II, there appears to be a defect in energy production or conservation. In anemia, myocardial failure results in insufficient transport of oxygen for substrate metabolism, while in hyperthyroidism uncoupling of oxidative phosphorylation may lead to failure of energy conservation. In beriberi heart disease a deficiency of thiamine pyrophosphate (cocarboxylase) produces a breakdown of certain specific decarboxylation reactions that appear to interfere with normal myocardial energy production. In hemorrhagic shock and myocardial infarction, general or localized anoxia leads to defective energy production.

Spontaneous failure occurring in the heart-lung preparation is in all likelihood the result of diminished catecholamine and cholinergic substances of the perfusion fluid.

It is apparent from this review that no common denominator exists as a cause of heart failure. Rather at the base of the uniform dynamic manifestations of this condition are multifarious disturbances in energy production, conservation, and utilization.

Conclusion in Interlingua

Investigationes del 3 phases del metabolismo cardiac—production de energia, conservation de energia, e utilisation de energia—ha revelate marcate differentias in le subjacente mechanismos de disfallimento cardiac. Assi, in disfallimento con prolongate supercargation del myocardio—como illo occurre in hypertension, morbo de valvula cardiac, e morbo arteriosclerotic del corde (hic designate como morbos de gruppo I)—le presentia de un anormalitate in le utilisation de energia es multo probabile. In le diverse situationes associate con disfallimento cardiac le quales es hic considerate sub gruppo II, il pare occurrer un defecto in le conservation o in le production de energia. In anemia, disfallimento myocardial resulta in un insufficiente transporto de oxygeno pro le metabolismo de substrato, durante que in hyperthyroidismo le discopulation de phosphorylation oxydatori pote resultar in un disfallimento del conservation de energia. In morbo cardiac beriberi, un deficientia de pyrophosphato de thiamina (cocarboxylase) produce un collapso de certe specific reactiones de discarboxylation e isto pare disturbar le normal production myocardial de energia. In choc hemorrhagic e in infarcimento myocardial, anoxia general o localisate resulta in un production defective de energia.

Le disfallimento spontanee que occurre in le preparato de corde e pulmon es probabilissimemente le resultato de un reducite contento de catecholamina in le liquido perfusional.

Iste revista rende apparente que nulle denominator commun existe in le causas de disfallimento cardiac. Al contrario, al base del uniforme manifestationes dynamic de iste condition il ha multiple disturbationes in le production, le conservation, e le utilisation de energia.

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The Kidney in Congestive Heart Failure

By A. C. Barger, M.D.

THE principal concern in the treatment of congestive heart failure must be, as Blumgart and Zoll emphasize,[1] the improvement of cardiac function. Therapy directed toward increasing salt and water loss by drugs acting primarily on the kidney may be life-saving, but does not, per se, lead to alterations in the basic abnormality. As a more detailed picture of the pathogenesis of the syndrome begins to evolve,[2-5] it is becoming apparent that the sodium and water retention of congestive heart failure is not a unique process, but is similar to that observed in other types of circulatory insufficiency. More recent investigations[2, 3, 6] have begun to clarify the reflex mechanisms, both nervous and hormonal, which link the decrease in cardiac competence and the consequent impairment of the renal excretion of salt and water.

Historically, the emphasis on the role of the kidney in the pathogenesis of the edema of congestive heart failure can be traced to Withering.[7] Although he noted an effect of foxglove on the "motion of the heart," the copious diuresis produced by the drug directed his attention to its renal rather than its cardiac effects. Subsequent work has shown that digitalis does have some direct effect on the kidney,[8, 9] but its efficacy in the treatment of congestive heart failure lies primarily in its cardiotonic action.[10] The chain of events by which improvement in cardiac function produced by digitalis leads to diuresis and natriuresis is discussed below.

The importance of dietary restriction of salt intake in the treatment of the edema of congestive failure has been stressed for many years. Although Karrell,[11] whose milk diet is still widely used,[1] commented in 1866 that "dans les cas même où l'hydropisie provient de l'lésion organiques du coeur . . . j'ai souvent constaté des améliorations très-sensibles et d'assez longue dureé," he was not aware that the low sodium content of the diet was the essential factor. Vaquez and Digne,[12] in 1905, however, described the causal relationship between increased sodium chloride intake and progressive accumulation of fluid in congestive heart failure, and recommended a low-salt diet. The significance of these observations of Vaquez and Digne was not fully appreciated until Schroeder's report in 1941[13] of the reduced urinary sodium chloride excretion of patients with congestive failure and persistent edema. The demonstration by Futcher and Schroeder[14] that mercurial diuretics, which depress tubular function, produced a marked increase in sodium chloride excretion led them to propose that the increased tubular reabsorption of sodium was the renal defect responsible for the salt retention and subsequent edema formation. Merrill,[15] on the other hand, impressed by the low glomerular filtration (inulin clearance) frequently observed in patients with severe congestive failure, postulated that as a result of the lowered filtration rate, a smaller quantity of sodium was delivered to the renal tubular cells. Assuming that these cells had a normal reabsorptive capacity, there would be more complete reabsorption of the filtered sodium, and hence sodium retention. However, not all the edematous patients studied by Merrill had diminished filtration rates, an observation verified by other investigators.[16, 17] Furthermore, clinical improvement, with increased sodium excretion, and loss of edema may occur without any rise in the depressed filtration rate.[16]

Studies in animals with surgically induced

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alvular damage of the heart have demonstrated that alterations in sodium metabolism occur very early in heart disease, at a time when basal glomerular filtration rate is still unchanged.[18, 19] Thus early in cardiac failure increased tubular reabsorption may be of primary importance in the sodium retention. More direct and conclusive evidence for the increased reabsorption of sodium has been obtained by the unilateral, intrarenal infusion of hypertonic saline.[20] In the normal dog unilateral sodium excretion rises many fold during such an infusion. In the dog in frank congestive failure, however, unilateral sodium excretion does not rise, even in the presence of a normal glomerular filtration rate. The efficacy of a mercurial diuretic, which depresses tubular function, in promoting a diuresis and natriuresis in such an animal is indicated in fig. 1. The intrarenal infusion of Thiomerin (mercaptomerin sodium) produced a unilateral, 40-fold rise in sodium chloride excretion on the ipsilateral side with the excretion rising from 5 μEq. per minute to over 200 μEq. per minute. Thus, at the peak of the natriuresis approximately 0.5 Gm. of sodium chloride per hour was being excreted from one kidney of a dog with frank congestive failure and ascites.

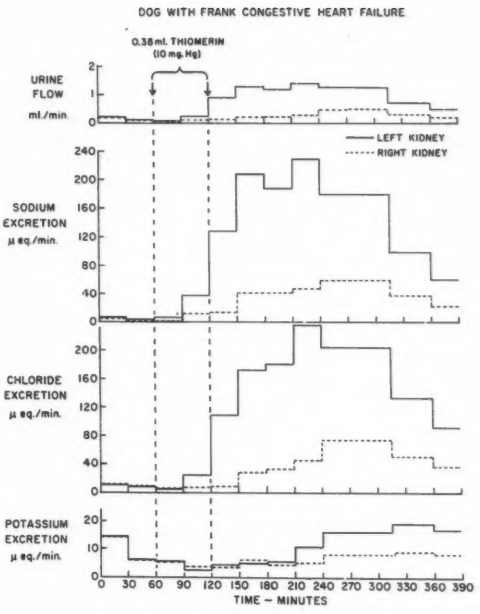

Figure 1

Effect of left intrarenal artery infusion of Thiomerin (mecaptomerin sodium) on sodium, chloride, potassium and water excretion in a dog with frank congestive heart failure (tricuspid insufficiency and pulmonary artery stenosis). Thiomerin (0.38 ml.) was infused for the 1 hour, indicated by the arrows and the broken vertical lines.

As the clinical condition of the patients with congestive heart failure deteriorates, glomerular filtration rate falls in most cases, both human and canine. The decreased filtration rate observed in this late stage undoubtedly enhances the sodium retention, and leads to more rapid accumulation of fluid. However, the sequence of events in the pathogenesis of sodium retention in congestive failure would appear to be (a) increased tubular reabsorption early in the disease, and (b) at a later stage the added factor of a lowered filtration rate. The reduced filtration rate is the result of the progressive renal vasoconstriction.

The studies by Merrill,[15] in 1946, had clearly shown that renal plasma flow (PAH clearance) was reduced even more markedly than the glomerular filtration rate in patients with frank, congestive failure, an observation that had been suggested by the earlier work of Seymour, Pritchard, Langley and Hayman.[16] A filtration fraction $\frac{\text{(inulin clearance)}}{\text{PAH clearance}}$ of 0.4 or more was frequently noted. In other types of circulating stress in which there is a reduction in "effective circulating blood volume," or a tendency for a decrease in arterial pressure, a similar decrease in renal plasma flow is observed, and is accompanied by sodium retention. For example, renal blood flow and sodium excretion are reduced by mild hemorrhage, or by quiet standing on the tilt table. Under such conditions baroreceptor (carotid sinus, aortic arch, etc.) activity is decreased, leading to reflex vasoconstriction and a restoration of blood pressure toward normal. It was therefore suggested several years ago[20] that the baroreceptor reflexes may play an important

role in the reduced renal blood flow and sodium retention of congestive heart failure.[2]

The possibility that increased activity of the renal nerves was responsible for the renal vasoconstriction and diminished blood flow in congestive failure was explored by Mokotoff and Ross in 1948.[21] They determined renal plasma flow and glomerular filtration rate in patients with congestive failure before and after the induction of spinal anesthesia high enough to block the renal nerves. Renal hemodynamics were, however, unaltered by the procedure. They concluded, therefore, that a neurogenic mechanism is not required for the maintenance of increased tone of the renal arterioles in congestive failure. However, using a more direct approach in unanesthetized dogs, Barger, Muldowney, and Liebowitz[2] have demonstrated that the infusion of an adrenergic blocking agent (Dibenzyline) directly into one renal artery of a dog with mild valvular heart disease leads to an increased renal plasma flow and a marked increase in sodium excretion on the infused side. Such an infusion produces little or no effect in the normal animal. Thus, increased sympathetic tone in the kidney occurs early in heart failure, and may be responsible in large measure for the increased tubular reabsorption of sodium seen early in heart disease. The mechanism by which the increased sympathetic activity leads to increased tubular reabsorption of sodium is still to be clarified. However, as the disease progresses the sympathetic tone increases markedly, leading to further diminution of renal blood flow, with a smaller decrement in filtration rate, and hence a further rise of filtration fraction to 0.4 or more. Such a filtration fraction implies an abnormally high colloid osmotic pressure in the first portion of the peritubular capillaries. Whether such a force may tend to accelerate the tubular transport of the filtrate still is not clear. A strong case for such a mechanism has been presented by Vander et al.[22]

In recent years great emphasis has been placed on increased aldosterone secretion as the mechanism responsible for the increased tubular reabsorption of sodium in congestive heart failure.[23] However, the exact role of aldosterone in the fluid retention of congestive failure still remains to be clarified, for increased aldosterone excretion has not been observed in all cases of congestive failure human[24] or canine.[25] Moreover, edema is not noted in patients with primary aldosteronism in whom higher aldosterone levels are found than in patients with congestive failure. Furthermore, direct infusion of aldosterone into one renal artery of a normal dog[26] produced a unilateral kaluresis, but did not lead to retention of sodium. In the adrenalectomized dog, however, both a kaluresis and an antinatriuresis are observed with intrarenal aldosterone. Similarly, intrarenal infusion of aldosterone in dogs with valvular damage leads to an increased potassium excretion and a decreased sodium excretion, suggesting an altered sensitivity to aldosterone in the presence of cardiac incompetence. The work of Davis, Howell, and Hyatt,[27] would appear to support the view that the kidney of the dog with congestive failure is more sensitive to mineralocorticoids. Adrenalectomized dogs that had been maintained in sodium balance with 3 mg. of desoxycorticosterone acetate per day (plus 25 mg. of cortisone) needed only 1 mg. of desoxycorticosterone acetate a day (plus 25 mg. of cortisone) to remain in sodium balance after the production of congestive failure, regardless of the level of glomerular filtration rate.

Thirty years ago, Goormaghtigh and Elaut[28] reported that denervation of the carotid sinus led to hypertrophy of the zona glomerulosa of the adrenal cortex, the site of aldosterone production. Although these observations have been verified by a number of subsequent investigators, the findings have attracted little attention in the search for the mechanism regulating aldosterone secretion. Similar hypertrophy of the zona glomerulosa is found in dogs with valvular heart disease. Such observations suggest that the baroreceptors may be responsible in congestive failure for both the increased sympathetic activity of the kidney and the increased aldosterone secre-

tion from the adrenal cortex. Recently, Bartter et al.[6] have presented evidence for the role of the baroreceptor nerves in the regulation of aldosterone secretion. Thus, in a dual manner, the pressoreceptor reflexes may play an important part in both the nervous and hormonal influences on the renal adjustments of fluid volume. Such a view emphasizes the compensatory role of the sodium retention of congestive failure, as suggested by Starling,[29] Peters,[30] and Landis et al.[31] Thus, therapy directed toward improving cardiac function would lead to increased baroreceptor activity and reflexly to decreased sympathetic tone in the kidney, diminished aldosterone secretion, and consequent increase in renal excretion of salt and water.

Summary

As a more detailed picture of the pathogenesis of salt and water retention in congestive heart failure evolves, it appears that increased tubular reabsorption of sodium occurs very early in heart disease, with further enhancement of the fluid accumulation as filtration rate decreases later in the disease process. Increase in sympathetic activity in the kidney can be demonstrated before the development of frank failure, and probably is initiated reflexly by decreased baroreceptor activity, a response that occurs in various types of circulatory insufficiency. Blocking the adrenergic nerves of the kidney produces profound diuresis and natriuresis. Evidence is presented that the pressoreceptors may also play an important role in regulating aldosterone secretion. Thus, the change in body fluids seen in congestive heart failure may be part of the normal reflex adjustments maintaining blood pressure.

Summario in Interlingua

In le curso del progressive clarification del pathogenese del retention de sal e aqua in congestive disfallimento cardiac, il ha devenite apparente que un augmento del re-absorption tubular de natrium occurre multo precocemente in le genese de morbo cardiac e es sequite per un promotion additional del accumulation de liquido quando le filtration es relentate plus tarde in le processo pathologic. Un augmento del activitate sympathic in le ren pote esser demonstrate ante le disveloppamento de disfallimento franc e es probabilemente initiate reflexemente per le reducite activitate baroreceptori. Isto es un responsa que occurre in varie typos de insufficientia circulatori. Blocar le nervos adrenergic del ren produce marcate grados de diurese e natriurese. Es presentate datos que indica le possibilitate que etiam le pressoreceptores ha un rolo importante in le regulation del excretion de aldosterona. Assi le alteration del liquidos corporee que es incontrate in congestive disfallimente cardiac es possibilemente un parte del normal adjustamentos reflexe que servi a mantener le tension del sanguine.

Acknowledgment

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CLINICAL PROGRESS

Paroxysmal Atrial Tachycardia with Block

By BERNARD LOWN, M.D., NORMAN F. WYATT, M.D., AND HAROLD D. LEVINE, M.D.

THE digitalis drugs can produce nearly every form of disturbed heart rhythm. Thus far clinical attention has been directed to the ventricular effects. Digitalis-induced ventricular arrhythmias are therefore clearly catalogued and are recognized as of potentially grave significance. Recent studies indicate that certain atrial disorders are also manifestations of serious digitalis poisoning.[1] The prototype of these atrial arrhythmias is paroxysmal atrial tachycardia with advanced degrees of atrioventricular (A-V) block (referred to as PAT with block). This has been regarded as a hybrid disorder of rhythm exhibiting features of both atrial flutter and atrial tachycardia. As in atrial flutter A-V block occurs either spontaneously or as a result of vagal stimulation. As in atrial tachycardia the ectopic rate ranges from 150 to 250 per minute (fig. 1).

A review of the literature suggests that PAT with block is an unusual disorder of uncertain etiology. Some of the leading cardiologists of our era have reported either isolated examples or small series of cases.[2-10] The general view has been that PAT with block is a variant of atrial flutter. Much discussion has centered on the nature of the atrial mechanism, whether it is due to a circus movement or to a repetitively discharging single focus. The etiology as well as the mechanism has remained obscure. Some have regarded it as a manifestation of severe digitalis intoxication,[5] others have suggested digitalis as the definitive treatment.[6]

Recent studies[1] indicate that PAT with block is a common arrhythmia of increasing frequency. In the majority of instances digitalis is the etiologic agent. The electrocardiographic features are distinctive and generally permit differentiation from other atrial disorders. When digitalis drugs or diuretic regimens are continued in its presence, the patient's life may be jeopardized. When PAT with block is recognized and the etiologic role of digitalis is appreciated, specific measures are available that permit restoration of a normal mechanism.

General Aspects of Digitalis Intoxication

Before PAT with block is discussed, certain aspects of the wider problem of digitalis intoxication need examination. The sensitivity to digitalis varies markedly from patient to patient and at different times in the same patient. Among the factors that determine the cardiac sensitivity to digitalis are the patient's age, the presence and extent of myocardial disease, the presence and degree of heart failure, the concomitance of hepatic and renal dysfunction, and the occurrence of electrolyte derangements

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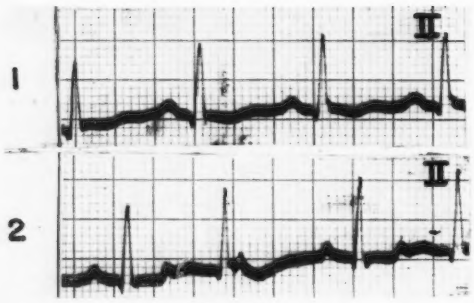

Figure 1

Normal sinus mechanism (1) compared with PAT block (2) with atrial rate of 150 in same individual. Note change in contour of P wave.

The heart of the newborn animal is resistant to digitalis-provoked ventricular arrhythmias. A high tolerance for digitalis has also been found in children before the age of 2.[11] Sensitivity to digitalis increases with advancing age. The integrity of the cardiovascular apparatus is another key factor which determines sensitivity to the drug. Individuals with normal hearts can tolerate massive doses of digitalis. Attempts at suicide with this drug have been unsuccessful in the absence of heart disease. A recent case report provides striking illustration of this fact.[12] The patient, a 36-year-old woman without heart disease, consumed at one time a dose of 50 mg. of digitoxin (Digitaline Nativelle). While subjective and atrial effects were prominent, no alterations in the ventricular complex were noted, and recovery was uneventful. In the presence of heart disease ventricular ectopic beats are common and are readily produced by digitalis. In the presence of heart failure the amount of digitalis required for full therapeutic effect constitutes 60 per cent of the potentially toxic dose. With increasing severity of heart failure, this narrow margin of safety is further reduced. In the end stages of cardiac decompensation beneficial drug action may be purchased only at the cost of a toxic response. At times toxicity precedes therapeutic action and precludes the use of digitalis entirely.

The diseased myocardium may only be partly responsible for the augmented sensitivity to digitalis. Alterations in hepatic and renal function that accompany heart failure may be contributory or even determining factors. The liver concentrates the largest fraction of administered digitoxin. It is probably a major site for digitalis binding and inactivation. For example, while ventricular arrhythmias can be readily produced in animals by the intravenous administration of acetylstrophanthidin, this is not the case when the drug is injected directly into the portal venous system.[13] In this latter instance massive doses of the drug may be administered without untoward effect on the heart. Liver injury reduces the lethal dose of strophanthidin in the rat.[14] Deranged liver function, which is an inevitable concomitant of heart failure, may thus expose the myocardium to higher concentrations of the active principle.

In heart failure there are also important deviations in renal function characterized by reduction in the renal plasma flow, in the glomerular filtration rate, and in tubular excretory and secretory functions. The kidney constitutes the major route for digitalis excretion. In patients with uremia, digitalis sensitivity is a common finding. Impaired urinary excretion may therefore play a role in the augmented digitalis sensitivity encountered in heart failure.

The cardiac threshold to digitalis depends also upon the state of body electrolyte distribution. While calcium has been shown in animal studies to modify the action of digitalis, in patients with heart failure the key ion appears to be potassium. Administration of potassium prevents and abolishes arrhythmias due to digitalis. Conversely depletion of potassium, no matter how produced, sensitizes the heart to digitalis. In the presence of potassium deficit, even small maintenance doses of digitalis may result in advanced intoxication.[15] Animals depleted of potassium respond to digitalis in some respects like animals in heart failure without evident electrolyte derangements. In both, the dose of digitalis for a toxic end-point is reduced, the duration of toxicity is prolonged, and multi-

orm ventricular mechanisms are common.

Electrolyte and water abnormalities accompany heart failure. These are due both to derangement in heart function and to the therapeutic procedures in current use. The development of cardiac decompensation is associated with a negative balance of potassium. Furthermore, therapeutic measures, such as rigid salt restriction and diuretic agents, favor renal potassium loss. The development of digitalis intoxication following a mercurial-induced diuresis results from such depletion of potassium. In the patient with heart failure potassium depletion is not commonly reflected in the serum concentration. Thus the serum potassium concentration generally affords no guide to the myocardial sensitivity to digitalis.

From the above considerations it would follow that digitalis intoxication may occur in the absence of an absolute overdose of drug. In clinical practice, indeed, serious toxicity frequently occurs while the patient is receiving constant maintenance therapy. The precipitating event is either deterioration in cardiac compensation or emergence of potassium depletion. Since the development of the former is subtle and the occurrence of the latter is not readily determined, it is at times difficult, if not impossible, to recognize digitalis intoxication. It is not surprising, therefore, that the role of digitalis in the promotion of atrial arrhythmias such as PAT with block has not been widely appreciated.

Selection of Material

The authors have concerned themselves with the digitalis-provoked atrial arrhythmias for nearly a decade. The body of this report is therefore based on personal experience.[1] The conclusions reached are being corroborated by others.[15-17] Differences of opinion wherever they exist are noted.

In the years from 1942 through 1954, 88 patients exhibiting 112 episodes of PAT with block were found in the records of the Peter Bent Brigham Hospital. This material was selected from the 51,722 electrocardiograms recorded during the 13-year period. Electrocardiograms were chosen for study if they exhibited 3 features: an atrial rate ranging from 150 to 250, an isoelectric baseline between P waves in all leads, and the existence of atrioventricular block beyond simple prolongation of the P-R interval. The case records were studied independently with a view to judging the state of digitalization at the time of the arrhythmia. Detailed temporal correlation was then made between changes in digitalis dosage, diuretic measures, serum electrolyte levels, and alterations in the eletrocardiogram. Digitalis was regarded as an etiologic factor in the development of PAT with block when any one of the following criteria was fulfilled: (1) if the arrhythmia developed during digitalization or after an increase in maintenance dosage and was abolished by discontinuing the drug; (2) if the arrhythmia occurred in a digitalized patient immediately after a mercurial-induced diuresis with a weight loss in excess of 1 Kg.; (3) if the arrhythmia appeared after procedures known to enhance digitalis effect, such as potassium loss induced by vomiting, diarrhea, hemodialysis; (4) if there emerged subjective and objective stigmata of digitalis overdosage in conjunction with the development of PAT with block which disappeared on discontinuing digitalis.

Deliberate studies of the development and recession of this disorder were also carried out. The continuous evolution of the arrhythmia was observed in 5 patients who were receiving acetylstrophanthidin, a very rapidly acting strophanthin derivative, given with the object of determining the status of digitalization.[18] The complete sequence in the recession of PAT with block was observed in 33 patients, during the administration of potassium chloride in 23 and of procaine amide in 10.

Role of Digitalis

At the outset it should be emphasized that PAT with block may be precipitated by factors other than digitalis. The present discussion is limited to the group in which PAT with block was presumed to be caused by digitalis. The basis for this presumption needs critical examination. Direct evidence that digitalis may provoke this arrhythmia is pro-

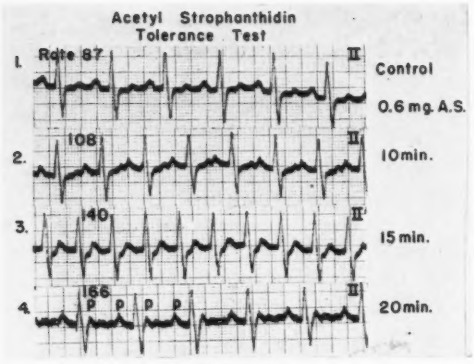

Figure 2

Induction of PAT with block by acetylstrophanthidin in over-digitalized patient. First clues to arrhythmia are change in contour of P wave and acceleration of atrial rate (strip 2).

vided by the digitalis tolerance test.[18] This test is accomplished by giving small increments of acetylstrophanthidin intravenously until either a therapeutic or toxic end-point is reached. PAT with block emerged in 5 of 50 patients thus tested. Acetylstrophanthidin was the only medication administered immediately prior to the onset of the ectopic mechanism. The arrhythmia was fully established within 1 to 20 minutes after the injection. The phases in the evolution of PAT with block were nearly identical in each of the 5 patients. The first harbinger of the arrhythmia (fig. 2) consisted of an acceleration of the atrial rate and alteration in size and contour of the P wave. As larger increments of acetylstrophanthidin were injected, or with the developing effect of the initial injection, the atrial rate increased and the P-R interval lengthened. At a critical atrial rate the A-V conduction deficit further increased and the 1:1 A-V response gave way to advanced degrees of A-V block. This experience therefore demonstrates that toxic doses of digitalis can produce PAT with block.

How frequently is digitalis a factor in initiating PAT with block? Data are provided from classification of the 88 patients on the basis of the previously enumerated criteria (table 1). Patients were classified into 1 of 3

Table 1

Classification of 112 Episodes of Paroxysmal Atrial Tachycardia with Block in 88 Patients on the Basis of the Etiologic Role of Digitalis

Group	Etiologic role of digitalis	Patients	Episodes	Per cent of total patients
I	Definite	64	83	73
II	Doubtful	11	16	13
III	Nonexistent	13	13	15

groups depending upon the role of digitalis. In the first and largest group (group 1), comprising 73 per cent of the patients, digitalis appeared to be related to the onset of PAT with block. In nearly all patients in this group more than one of the 4 criteria implicating digitalis was satisfied. In a second group (group II), consisting of 11 digitalized patients (12.5 per cent) either the role of digitalis was less certain or a cogent alternative explanation for the arrhythmia was apparent. In the last group (group III), consisting of 13 patients (15 per cent), either digitalis was never taken or PAT with block developed prior to digitalization.

The role of digitalis as a cause of PAT with block in the first group was supported by the frequency of subjective and objective stigmata associated with digitalis overdosage. Symptoms of digitalis intoxication were noted in over a third of the patients. In over half, electrocardiographic evidence suggesting overdigitalization was also detected. The most common finding was ventricular premature beats, which were frequently multiform and at times bigeminal (fig. 3). In 18 episodes first-degree A-V block and in 5 complete heart block was present either immediately before or shortly after a bout of PAT with block.

It has been emphasized earlier that digitalis intoxication may occur without changes in its maintenance schedule. Frequently depletion of body potassium is the precipitating factor; this is especially true in the pathogenesis of PAT with block. The role of potassium loss in provoking the arrhythmia was most clearly illustrated during artificial hemodialysis of digitalized and nondigitalized patients.[18] In

Table 2

Factors Precipitating 83 Episodes of Paroxysmal Atrial Tachycardia with Block in 64 Digitalized Patients

Immediate cause	Number of episodes	Per cent
Digitalis overdose	24	29.0
Mercurial diuresis*	31	37.2
Sensitivity to digitalis	9	10.8
Miscellaneous†	19	23.0

*Also included are those with overdose who simultaneously sustained a substantial diuresis.

†Includes potassium losing procedures such as hemodialysis, vomiting, cortisone, etc.[1]

17 patients who had not received digitalis, potassium extraction produced no arrhythmias. In the 16 patients who were digitalized, potassium removal by means of an artificial kidney provoked arrhythmias in 7, in 3 assuming the form of PAT with block. The phases in the development of PAT with block during potassium extraction were similar to those occurring during the administration of acetylstrophanthidin (fig. 4*B*).

Losses of potassium appeared to play a significant role in the precipitation of PAT with block in patients in group I (table 2). In 37 per cent, a mercurial-induced diuresis was the factor immediately preceding the arrhythmia, whereas in 23 per cent, constituting the miscellaneous group, hemodialysis, renal potassium loss, cortisone administration and other factors known to promote loss of potassium from the body, were implicated. Thus in 60 per cent of PAT with block due to digitalis, alteration in the balance of body potassium was the key factor.

The efficacy of potassium in abolishing PAT with block when induced by digitalis further illustrates the relationship between glycoside and cation. Episodes of PAT with block not due to digitalis are unaffected by the administration of potassium.[1] When PAT with block has been precipitated by diuretic therapy or an overdose of digitalis, potassium invariably restores a normal mechanism. The sequence of electrocardiographic events is a chronologic mirror image of the phases in the emergence of PAT with block (fig. 4*C*).

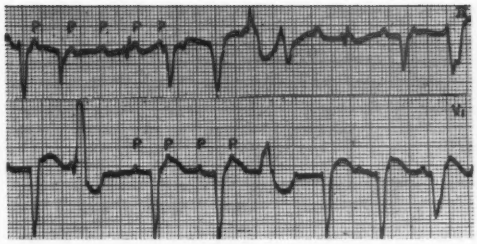

Figure 3

Coexistence of PAT with block with other electrocardiographic stigmata of over-digitalization (multiform repetitive ventricular premature beats).

Initially there occurs a slowing of the atrial rate; there then follows a resumption of 1:1 A-V conduction. At a critical rate, generally ranging from 105 to 150, there is an abrupt change in pacemaker with resumption of sinus rhythm.

Three lines of evidence, therefore, indicate that digitalis is the common etiologic factor of PAT with block: (1) the frequent onset of the arrhythmia during initial digitalization or after increases in maintenance dosage; (2) the concurrence in the majority of patients having PAT with block of the well-recognized subjective and objective stigmata of digitalis intoxication; (3) the operation of the digitalis-potassium relationship, namely the provocation of PAT with block by potassium-depleting procedures and the abolition of this disorder by potassium supplementation.

It is now generally accepted that PAT with block may result from excessive digitalis. Differences of opinion concern only the relative role of digitalis in precipitating this arrhythmia.[15, 17, 19, 20] It is to be emphasized that when the same criteria were employed for diagnosing this arrhythmia, nearly identical conclusions on the role of digitalis in the pathogenesis of PAT with block were reached in widely separated places.

Clinical Factors

The following discussion is based upon a group of 64 patients exhibiting 83 episodes of PAT with block caused by digitalis.[1] The majority of patients were in advanced stages

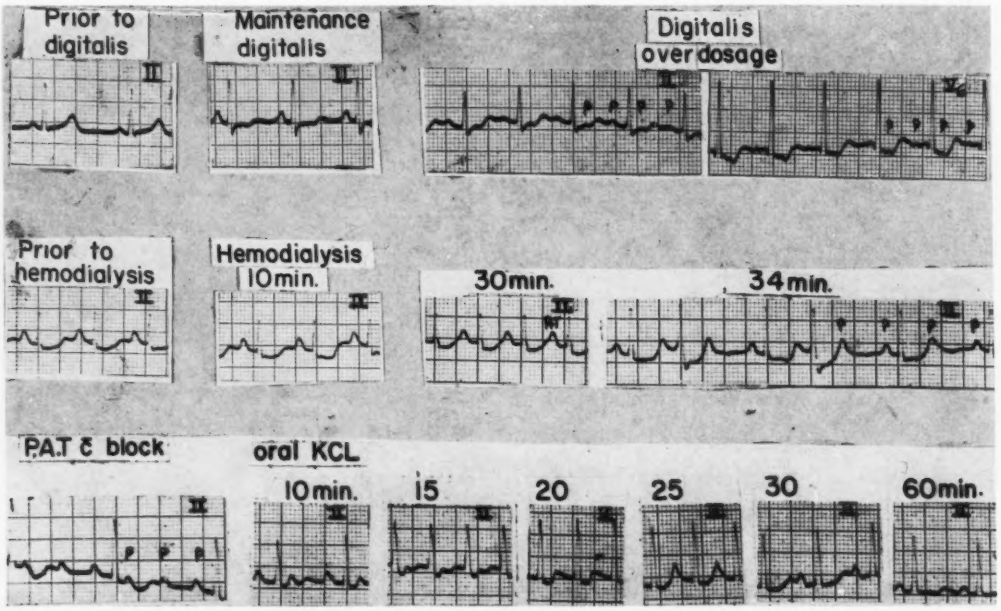

Figure 4

Demonstration of the digitalis-potassium relationship. Top. *Induction of PAT with block by digitalis. Overdose of Digoxin induces the arrhythmia.* Middle. *Induction of PAT with block by removal of potassium ion. Similar sequence on removal of potassium by means of hemodialysis in patient on small maintenance digitalis therapy.* Bottom. *Elimination of PAT with block by administration of potassium ion. The sequential phases in the abolition of PAT with block by means of potassium.*

of congestive heart failure. The sodium intake was therefore restricted and frequent diuretic injections were administered. The mean age of this population was 51 years. There was a slight preponderance of females. Ten of the patients were in uremia (fig. 5). Rheumatic, hypertensive, and coronary artery disease figured about equally as the basis for the heart failure. Twelve patients experienced more than one episode of the arrhythmia. In only a third of the patients was a definite overdose of digitalis given prior to the onset of PAT with block. The remaining two thirds were receiving maintenance doses of digitalis; in these the arrhythmia was precipitated by potassium-depleting procedures or by an unusual sensitivity to the drug (table 2).

As the patient who experiences PAT with block is already severely ill, the onset of the arrhythmia may add but little to the clinical picture. Generally the clinical state is modified in 1 of 3 ways: by the aggravation of congestive heart failure, by the acceleration of the heart rate, and by the development of manifestations of digitalis overdosage. Deterioration in the cardiac status may occur even when the ventricular rate is not rapid. The heart rate usually exceeds 100 beats per minute, the result of persistent or transient 1:1 response. On auscultation PAT with block may be characterized by gross irregularity of ventricular rhythm indistinguishable from atrial fibrillation; this is due to the variability in A-V conduction and the irregularity between successive P waves. If the period of auscultation is prolonged, periodic regularity in rhythm may be noted. Symptoms of digitalis intoxication are found in at least a third of patients. Ventricular ectopic beats, uniform or multiform, occur in nearly half the pa-

ients. The usually accepted stigmata of digitalis intoxication may occur at times, either before the onset or immediately after the offset of PAT with block.

No specific clinical signs exist for the recognition of PAT with block. Occasionally the presence of varying A-V block is suggested by the changing intensity of the first sound. Regularization of a previously irregular rhythm is at times the first clue. In patients with sinus rhythm the converse change, namely irregularity of a previously regular rhythm, especially when it occurs in the wake of intensive diuretic measures or increasing doses of digitalis, may be the first suggestion of the development of PAT with block.

With the exception of the patients subjected to hemodialysis, the onset of PAT with block bore no relation to the serum concentration of potassium. Abnormal potassium values were unusual. Only 10 per cent of patients with the arrhythmia had serum potassium levels below 3.0 mEq. per liter. The mean potassium concentration during the arrhythmia was 4.2 mEq. per liter (for a group of 30 patients). The serum sodium concentration ranged from 120 to 130 mEq. per liter in a third of patients; in the remainder it was normal. Serum chloride and bicarbonate values were generally within the normal range. Thus the majority of patients with PAT with block do not exhibit derangement in serum electrolytes.

A grave prognosis attends the digitalis-induced variety of PAT with block. This prognosis is undoubtedly related to the underlying serious heart disease. The serious outlook is in addition determined by the failure to recognize the arrhythmia as a manifestation of digitalis intoxication. The most common error is to consider PAT with block as a variant of flutter and to administer more digitalis in an attempt to slow the heart rate. The reported mortality varies from 28 per cent[19] to 58 per cent.[11]

There is evidence suggesting an increase in the incidence of PAT with block.[1] When the frequency of this disorder was compared for 2 3-year periods, one in the 1940's and the second in the 1950's, the incidence rose from 10 to 42 episodes. This increase may have been due to the greater number of electrocardiographic tracings recorded in more recent years. When correction is made for this factor, however, a substantial increase in incidence is still evident. One episode of PAT with block was recorded in every 1,000 electrocardiograms in the 1940's as contrasted with 1 in 500 electrocardiograms during the 1950's.[1]

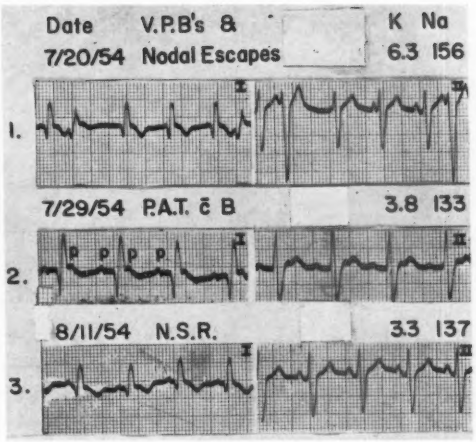

Figure 5

Induction of digitalis intoxication in patient, a 45-year-old man with preexistent myocardial infarction in uremia, on maintenance dose of digitoxin 0.1 mg. daily even though hyperkalemic (strip 1). *Development of PAT with block on resumption of digitoxin therapy* (strip 2). *Restoration of normal sinus mechanism on discontinuing digitoxin* (strip 3).

Electrocardiographic Features

The diagnosis of PAT with block rests ultimately upon the electrocardiogram. To appreciate the electrocardiographic features of this arrhythmia it is necessary to comprehend the arrhythmia not as a fixed pattern but rather as a dynamic process with varying phases. Judged by the contour of the P wave the site of impulse formation may be located anywhere in the atrium or A-V node. The arrhythmia may persist with a rate sustained well within the range ascribed to the sinus node. The lowest rate recorded in which the ectopic site was still dominant was 106. Usu-

ally the atrial rate ranges from 150 to 250; in three fourths of episodes it is less than 190 per minute.

Early in the development of this disorder spontaneous A-V block is absent. Usually a phase is reached in which the ectopic rate is above that of the range noted in sinus tachycardia. There is now a 1:1 A-V response with A-V block latent, i.e., the impaired conduction is demonstrable only by stimulation of the carotid sinus or other vagal measures. The usual form of the arrhythmia, however, manifests second-degree A-V block. The deficit in A-V conduction may be apparent as a sporadic Wenckebach phenomenon, more frequently as sustained 2:1 block. Even in the latter instance, if a sufficiently long strip is recorded, variation in A-V conduction may still be observed. More rarely, the degree of block may be complete, either transiently or continuously. Finally, the form of the arrhythmia may be that of 2 competing pacemakers, one in the atrium, the other in the A-V node.

In a considerable proportion of cases the P-P cycles vary in their duration. In nearly half of the episodes variation ranging from 0.02 to as long as 0.12 second is encountered. The P waves are generally upright in leads II and III and usually diminutive. In 15 per cent of episodes P waves are not demonstrable in the limb leads; in such cases lead CR_1 of V_1 may show atrial deflections. In the majority of episodes the P waves during PAT with block differ in contour from the sinus P waves. These differences are evident in the limb leads as well as in the precordial leads. A critical feature of PAT with block is the presence in all leads of an isoelectric baseline between P waves. Characteristic undulation of this baseline even in a single lead identifies the disorder as atrial flutter. This finding is of clinical value, for it indicates usually that the atrial arrhythmia is not due to digitalis intoxication.

The mechanism preceding the onset of PAT with block is generally normal sinus rhythm or sinus tachycardia. Irrespective of the antecedent rhythm, once PAT with block is controlled with potassium or procaine amide, a sinus mechanism is restored. This is true even of patients who have had chronic atrial fibrillation. In 1 unusual patient with atrial fibrillation, present continuously over 10 years and resistant to quinidine reversion, normal sinus rhythm was reestablished after control of a digitalis-induced episode of PAT with block. The sinus mechanism has now persisted for 3 years without the benefit of quinidine.

Differentiation from Other Arrhythmias

Paroxysmal atrial tachycardia with block is frequently missed or confused with other arrhythmias, either atrial or ventricular. This is clearly the result of the varying phases that the arrhythmia may assume in its development or recession.

Sinus tachycardia may be simulated during 2 phases of the arrhythmia, namely, when the ectopic pacemaker is discharging at a slow rate in the absence of heart block and also when 2:1 block exists but the nonconducted P wave is incorporated in the preceding T wave or QRS complex. When P waves are not discernible in the standard unipolar leads, nodal rhythm or nodal tachycardia is mistakenly diagnosed. Confusion with classical atrial tachycardia occurs when P waves are diminutive, the P-R interval is prolonged, or the heart rate exceeds 150 (fig. 6, strip 4). PAT with block may also simulate atrial fibrillation. The small atrial complexes, varying P-P cycles, and changing degrees of A-V block contribute to this error. It is evident that with an atrial rate of 200 to 250 and 2:1 A-V block, atrial flutter may be considered the underlying mechanism. When the 1:1 response-phase persists at a rapid atrial rate, bundle-branch block or other forms of aberrant ventricular conduction may prevail. In such a circumstance ventricular tachycardia may be considered as the underlying disorder.

The problem of the differentiation between PAT with block and atrial flutter deserves more detailed consideration. It should be emphasized that clinical implications as to the role of digitalis need be divorced from electrocardiographic analysis. There are forms of

PAT with block that are due to digitalis and some that are due to other factors. This distinction cannot be made on electrocardiographic grounds. Rarely atrial flutter is due to digitalis overdosage, although most commonly it is not. Here again the electrocardiogram sheds no light concerning the etiology of the arrhythmia. The same is true of all other disorders of rhythm. Ventricular bigeminy for example, which is regarded as a hallmark of digitalis intoxication, frequently occurs in patients who have never received digitalis. The finding of such a derangement in rhythm alerts the clinician to possible intoxication with digitalis. The same holds true for PAT with block. The ultimate decision as to the role of digitalis must rest on clinical grounds. Since over two thirds of cases of PAT with block are the result of an overdose of digitalis and less than 1 per cent of cases of atrial flutter have a like etiology, the crux of the problem is whether the 2 arrhythmias can be distinguished electrocardiographically.

In the majority of instances such differentiation is possible. In flutter the atrial rate generally exceeds 250. In a group of 40 patients recently studied the mean rate was 310. By contrast, in 83 episodes of PAT with block due to digitalis the average rate was 180. In only 6 episodes did the rate exceed 250.[1] In flutter, the atrial complex is inverted in leads II and III with a characteristic undulation of the baseline, which is apparent in these or other leads. In PAT with block the isoelectric baseline between successive atrial deflections is a sine qua non for the diagnosis. In PAT with block P waves are usually upright in the limb leads. Additional considerations that are helpful in the differentiation are the degree of A-V block, the cycle length, and the presence of ectopic beats. In untreated atrial flutter the atrioventricular response is usually 2:1. In PAT with block variability in A-V conduction predominates. This is evident if electrocardiographic strips of sufficient length are examined. In pure flutter the atrial rhythm is perfectly regular. In PAT with block such regularity is found in only half of the cases. Ventricular premature beats are frequent in association with PAT with block, less so in atrial flutter. In the latter, when abnormal ventricular complexes occur, they are frequently the result of aberrant ventricular conduction of impulses of supraventricular origin.

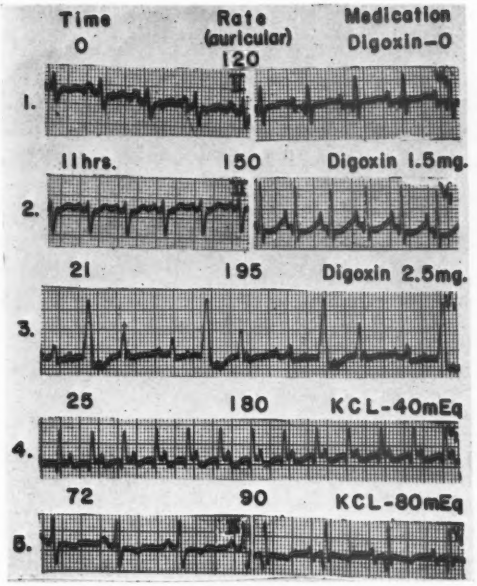

Figure 6

Evocation of early phase of PAT with block in 17-year-old boy with myocarditis by intravenous digitalization with 1.5 mg. of Digoxin (strip 2). *The nature of the arrhythmia was unrecognized; an additional 1.0 mg. of Digoxin given for increasing pulmonary edema* (strip 3). *Although apparently moribund* (strip 4) *uneventful recovery followed the administration of 80 mEq. of potassium chloride* (strip 5). *Note 1:1 response phase in strip 4.*

Critical differentiation between flutter and PAT with block can also be established by the response to administered potassium. A gradual and sequential slowing with recession of the arrhythmia is noted in PAT with block. In atrial flutter there is no resolution of the arrhythmia; at times the only result is a slight acceleration in the atrial rate. In an occasional patient the administration of potassium is the only means of clarifying the nature of the atrial disorder.

It is widely held[21] that the rate and the site of discharge of the atrial pacemaker determine the electrocardiographic pattern of atrial arrhythmias. The experience with PAT with block suggests that rate alone is not the critical determinant of the electrocardiographic morphology of the atrial complex. When a patient having PAT with block is given digitalis the atrial rate accelerates, at times reaching well within the rate range ascribed to flutter without change in the contour of the P waves or in the isoelectric baseline. Moreover, the rate in atrial flutter may be slowed by quinidine, potassium, or anoxia to a range customarily seen in sinus tachycardia, yet without a change in the characteristic undulant configuration which is exhibited at faster rates. In short, rapid PAT with block and slow flutter may retain their distinctive electrocardiographic forms. More convincing that rate is not the sole determining factor is the observation gained from the occasional patient experiencing both arrhythmias successively. At times atrial flutter manifests a slower rate than that which occurs with PAT with block. The features that distinguish PAT with block from flutter probably reflect fundamental differences in the mechanism of these 2 atrial disorders.

Therapy

When the arrhythmia is due to digitalis, it is mandatory to withhold this drug and omit diuretic measures until a normal mechanism is restored. Three agents are available for the rapid control of this disorder, namely, potassium, procaine amide, and disodium versinate. The choice of antidote and the manner of its use depend upon the clinical situation.

Treatment may be limited to discontinuing digitalis when the atrial rate is less than 170 and the cardiac status is not threatening. In patients with advanced congestive heart failure, especially when diuretic measures have precipitated the arrhythmia, the oral or intravenous use of one of the salts of potassium is indicated (fig. 6). When continuous electrocardiographic monitoring cannot be carried out during the administration of potassium, the oral route is preferred. The potassium requirements for reversion range from 20 to 120 mEq.; the average dose required is usually about 60 mEq. This may be given orally in a dose of 5 Gm. (67 mEq.). In order to diminish gastric irritation the potassium may be mixed with iced orange juice and administered over a 30-minute period. Oral potassium is effective within 15 to 30 minutes with peak action at 2 hours. If complete reversion has not been achieved within this interval a 2.5 Gm. dose may be repeated. If by the time a total of 7.5 Gm. (100 mEq.) has been ingested no material slowing of the atrial rate has occurred, further administration of potassium will prove ineffective. It is best at this juncture to reconsider the role of digitalis in the production of the arrhythmia.

When potassium is effective, a 1:1 A-V response invariably develops. If this is accomplished at a rapid atrial rate, the patient may feel uncomfortable and may even develop increasing evidence of left ventricular failure. The achievement of such a 1:1 response, though occasionally alarming, augurs well and indicates that therapy is on the right path. An additional dose of potassium will thereupon favor the resumption of normal sinus rhythm.

When the patient appears critically ill and it is feared that a prolonged 1:1 response phase may jeopardize survival, the intravenous route is favored. With competent electrocardiographic supervision this is safer than the oral route, for the infusion can be interrupted at the earliest evidence of potassium intoxication, namely when the tracing shows tenting or peaking of the T waves. By contrast, an oral dose, once ingested, cannot readily be removed. The dose for intravenous use is 40 mEq. (3 Gm.) diluted in 500 ml. of glucose in water given over the course of an hour or two. If slowing occurs but complete reversion is not accomplished, another 40 mEq. may be infused. Potassium when administered in the manner outlined above was successful in reverting 23 out of 25 episodes of PAT with block due to digitalis.

Procaine amide has proved to be an effective

agent in the control of PAT with block. It is widely recognized as an anti-arrhythmic drug which depresses myocardial excitability. Many of the arrhythmias that have been successfully treated with procaine amide were produced by an overdose of digitalis.[18] When it is used for PAT with block, the sequential phases in the reversion of the arrhythmias are indistinguishable from those that follow the administration of potassium (fig. 7). It may be that with more experience procaine amide will prove to be the drug of choice. For the time being it is indicated under the following circumstances: in the presence of uremia when potassium intoxication is likely; when the electrocardiographic tracing suggests hyperkalemia and electrolyte data are not available; when the patient's status is critical and prompt control is mandatory; and when large doses of potassium have already been administered but have not accomplished complete reversion. The intravenous route is preferred. Fifty milligrams may be given at 2-minute intervals. The blood pressure is determined prior to each increment. If there is a tendency to hypotension, the interval between doses is lengthened. Generally no more than 1 Gm. of procaine amide is required to achieve reversion.

A third method for the control of PAT with block is lowering the fraction of ionized calcium in the blood.[16, 22] The serum calcium can now be readily, safely, and rapidly reduced by means of disodium versinate, a metallic chelating agent. The resolution of the arrhythmia by this means is similar to that achieved by the administration of potassium. This is not surprising for a reciprocal relationship exists between calcium and potassium in their effect upon the automaticity of cardiac muscle. Considered from the point of view of cardiac excitability, reduction of ionized calcium is tantamount to increasing potassium. The experience to date with this agent is limited. Its precise role in the management of arrhythmias due to digitalis awaits further elaboration.

Once reversion has been achieved, the question of continuing suppressive potassium therapy needs to be considered. If the arrhythmia has resulted from diuretic measures, it is proper to employ prophylactic potassium in a dose of 3 to 5 Gm. on the day of and the day following diuresis. Continued maintenance potassium therapy in the presence of congestive heart failure is not without hazard. The patient who is on a rigid low-sodium diet appears to have a lesser tolerance to supplementary potassium. The more severe the degree of heart failure the greater is the likelihood of producing serious potassium intoxication, even when the daily increments of potassium are small. The reason for this may be that uptake of potassium by such tissues as the liver and skeletal muscle is impaired by anoxemia and the attendant circulatory changes of congestive heart failure. If the patient's threshold to the toxic effect of digitalis is low and a therapeutic effect cannot be sustained without the intervention of such arrhythmias as PAT with block, it may then be necessary to employ maintenance potassium dosage. In such a case periodic electrocardiograms as well as determination of serum electrolytes are in order.

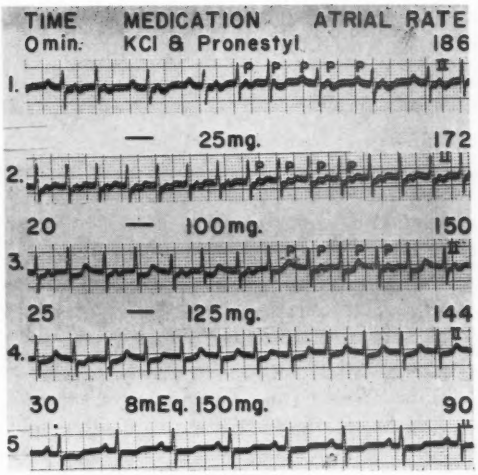

Figure 7

Resolution of PAT with block on the combined administration of potassium chloride and procaine amide. During previous bouts of the arrhythmia much larger doses of either potassium or procaine amide were required when used singly.

Mechanism and Pathogenesis

The cardiologic literature has been occupied with much discussion concerning the underlying mechanism of atrial disorders, particularly flutter. There are 2 schools of thought. Some consider that this rapid rhythm is sustained by a wave of excitation continuously traversing a circus pathway.[23, 24] Others believe that the impulses are discharged repetitively from a single focus and are transmitted equally in all directions.[21, 26] The proponents of the latter view maintain that the rate of impulse formation is a critical factor that determines the electrocardiographic features of flutter, as well as of other atrial tachycardias. Because of its similarity to flutter, the possibility of an underlying circus rhythm has been suggested for PAT with block.[6] This arrhythmia starts with a slow rate, usually below 150, and is thus within the range of discharge of the sinus node. This argues against a circus rhythm. At such slow rates the size of the pathway required would be too large to be accommodated by the dimension of the atrial chambers. If in the initial phases a circus mechanism is not operative, it is unlikely that this be true in the later phases, for the rate gradually accelerates without visible alteration in the atrial complex. The quiescent baseline between P waves in all leads is an additional argument against a continuous activation of atrial musculature. It is therefore likely that PAT with block is the result of a repetitively discharging single focus within the atrium.

Where then is the site of impulse formation? The answer to such a question when derived from clinical material is generally based upon an analysis of the contour, size, and direction of the atrial complex in various leads. It needs to be recognized that changes in the P wave may represent biochemical changes in the atrial musculature rather than alteration in the site of impulse formation. Vagal stimulation and various medications may induce changes in the P wave without displacing the pacemaker from the sinus node. If one accepts the usual electrocardiographic interpretation that change in the morphology of the P waves does denote a shift of the pacemaker from the sinus node, then this must be true in the majority of instances of PAT with block. The upright direction of the P wave in leads II and III would suggest that the impulse originates in the upper or cephalic region of the atrium. The fact that the atrial complex is generally diminutive and frequently resembles the sinus P wave would tend to locate the focus in proximity to the sinus node. In further support of an ectopic site for the arrhythmia is the failure of vagal measures to influence the atrial rhythm even when the rate is less than 150 per minute.

How then does digitalis change atrial rhythmicity and promote the development of PAT with block? Any analysis of the pathogenesis of this arrhythmia must take into account the possible role exerted by potassium depletion. The increasing incidence of this disorder in patients in congestive heart failure has been ascribed to the growing dependence of therapy upon electrolyte manipulation and consequent potassium deficits.[1] It is of interest that the electrocardiographic changes induced by selective potassium removal in animals resembles clinical PAT with block in many respects. These changes are further amplified by digitalization. The essential features are tachycardia and A-V conduction defect. The evolution and regression of both the human and animal arrhythmia consist of nearly analogous sequential phases. In clinical practice PAT with block is much less frequent than ventricular arrhythmias due to digitalis; yet it is noteworthy that, of 7 uremic patients who developed digitalis intoxication during or after potassium extraction by means of hemodialysis, 3 exhibited this atrial disorder. A majority of patients who develop PAT with block due to digitalis have been maintained on intensive diuretic measures. In many, a diuresis appeared to be the immediate and sole precipitating event. The observation that advanced decompensation is usually the background for this arrhythmia is not incompatible with the concept that de-

rangement in the potassium balance is a key factor. It has been established that potassium deficits may occur in the later stages of heart failure. Potassium may also play a role in the pathogenesis of PAT with block in patients who developed the arrhythmia after an overdose of digitalis in the absence of all diuretic measures or any demonstrable body losses of this cation. It has been shown that large doses of digitalis promote loss of heart muscle potassium.[27, 28] In effect, the common denominator to all digitalis-induced PAT with block may be a deficit of this cation within the myocardial cell. It is therefore pertinent to determine the mechanism by which a deficit of body potassium sensitizes atrial muscle to digitalis.

In experimental animals production of isolated deficits of potassium results in striking changes in the atrial complex. These consist of an increase in the amplitude of the P wave, an acceleration in the atrial rate, and emergence of first degree heart block.[29] The physiologic studies of Howell[30] have demonstrated a decrease in atrial responsiveness to vagus nerve action when the isolated mammalian heart is perfused in a medium devoid of potassium. Since loss of potassium does not inhibit the liberation of acetylcholine, the effect of such depletion must be to interfere with the action of the neurohumor on the sinus node. Impulse formation in the atria is under continuous vagus control; thus the removal of the tonic inhibition by deficit in potassium would result in an increase in height of the P wave and acceleration in atrial rate. The occurrence of A-V block in the presence of potassium depletion appears paradoxic. The hypothesis is offered that loss of potassium does not interfere with the action of acetylcholine upon the A-V node. In support of this supposition is the observation that in animals with severe potassium depletion, vagal maneuvers readily alter A-V conduction but not the atrial rate. Clinical electrocardiographic, physiologic, and biochemical differentiation between vagus effects upon the atrium and upon the A-V node is reviewed elsewhere.[1]

In the normally ennervated atrium the sinus rate is slowed by digitalis; this is due to the enhancement of tonic vagal action. Digitalis increases the automaticity of the atria when vagus action is abolished by vagotomy.[31] Under such circumstances the atrium responds to an overdose of digitalis, as does the ventricle, with ectopic mechanism

The digitalis-induced atrial tachycardia is dependent upon the sensitization of atrial muscle to cardiac glycosides which results from the reduction or removal of vagus action by potassium depletion. The A-V block is the result of 3 factors: the rapid atrial rate, the indirect or vagal effect of digitalis upon the A-V conduction system which is not disturbed by potassium deficit, and the direct action of digitalis in prolonging the refractory period of conduction in the A-V node and bundle. The interaction of these processes produces the composite electrocardiographic pattern of paroxysmal atrial tachycardia with block.

Summary and Conclusion

Disorders in atrial rhythm are relatively common and increasingly frequent accompaniments of digitalis intoxication. The usual electrocardiographic pattern of the atrial arrhythmias is paroxysmal atrial tachycardia (PAT) with block. The emergence of a change in rhythm after increasing doses of digitalis or active diuresis affords a clue to the possible presence of this mechanism. Confirmation rests upon the following electrocardiographic features: an atrial rate of 200 or less, a change in contour of the P waves, isoelectric baseline between atrial complexes, and variable degrees of atrioventricular block. In the phases of its development and recession PAT with block may simulate any of the atrial arrhythmias.

Potassium depletion favors the provocation of PAT with block by digitalis. The serum potassium level, however, is not abnormal. Restoration of a normal mechanism requires omission of digitalis, suspension of diuretic measures, and supplementation with potassium or procaine amide, either singly or in combination.

PAT with block is a unifocal atrial arrhythmia. The ectopic site is lodged in the cephalic

part of the atrium, probably in proximity to the sinus node. It has been conjectured that losses of potassium interfere with the vagus effect upon the atrium but not upon the A-V node. In the absence of vagus action upon the atrium, digitalis enhances atrial automaticity, provoking premature beats and tachycardia. Simultaneously both the direct and indirect (vagus) effect of digitalis on the A-V node is to delay conduction. The end result is PAT with block.

Summario in Interlingua

Disordines del rhythmo atrial es relativemente commun. Illos es crescentemente frequente como accompaniamento de intoxication per digitalis. Le usual configuration electrocardiographic del arrhythmias atrial es paroxysmic tachycardia atrial (PTA) con bloco. Le advento de alterationes de rhythmo post crescente doses de digitalis o post diurese active representa un signo del presentia possible de iste mechanismo. Le confirmation require le sequente phenomenos electrocardiographic: Un frequentia atrial de 200 o minus, un alteration de profilo del undas P, isoelectric linea base inter complexos atrial, e variabile grados de bloco atrioventricular. In le phases de su disveloppamento e de su regression, PTA con bloco es capace a simular omne arrhythmia atrial.

Depletion de kalium promove le production de PTA con bloco per digitalis. Tamen, le nivello seral de kalium non es anormal. Le restauration de un mechanismo normal require le omission de digitalis, le suspension del mesuras diuretic, e un supplementation de kalium o amido de procaina, individualmente o in combination.

PTA con bloco es un unifocal arrhythmia atrial. Le sito ectopic es locate in le parte cephalic del atrio, probabilemente in proximitate al nodo sinusal. On ha conjecturate que perditas de kalium disrumpe le effecto vagal super le atrio sed non super le nodo atrio-ventricular. In le absentia de un action vagal super le atrio, digitalis promove le automaticitate del atrio e evoca pulsos prematur e tachycardia. Simultaneemente, tanto le directe como etiam le indirecte (i.e. vagal) effecto de digitalis super le nodo atrio-ventricular consiste in retardar le conduction. Le resultato final es PTA con bloco.

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Parsons, W. B., Jr., and Flinn, F. J.: Reduction of Serum Cholesterol Levels and Beta-Lipoprotein Cholesterol Levels by Nicotinic Acid. Arch. Int. Med. **103**: 783 (May), 1959.

Serum cholesterol levels could be reduced in the majority of patients with hypercholesteremia by administering large doses of nicotinic acid, while the patients continued to eat their usual diets. The reduction was most prominent in the β-lipoprotein cholesterol fraction, with reduction of the β/α_1 lipoprotein cholesterol ratio. The only side effects after ingestion of the nicotinic acid were pruritus and flushing, which subsided rapidly in the stages of therapy and did not interfere with therapy. Because fatty metamorphosis had been reported in the livers of rats fed diets containing 1 per cent nicotinamide, a liver profile was obtained and a needle biopsy of the liver was studied in 17 patients after 1 year of therapy. Na significant toxic reactions were found by this or other clinical and laboratory observations. Nicotinamide was ineffective in reducing serum cholesterol levels. As yet the mechanism by which nicotinic acid reduces the level of blood cholesterol remains unknown. Furthermore, a much longer period of observation will be required to determine whether this form of therapy for hypercholesteremia will prevent or retard the progression of atherosclerosis in man as it does in cholesterol-fed rabbits.

Krause

ABSTRACTS

ATHEROSCLEROSIS

Boyer, P. A., Jr., Lowe, J. T., Gardier, R. W., and Ralston, J. D.: Effect of a Practical Dietary Regimen on Serum Cholesterol Level. J.A.M.A. **170**: 257 (May 16), 1959.

Three hundred institutionalized patients under conditions permitting rigorous control of diet were put on a regimen tending to lower blood cholesterol levels. The significant feature was the use of a margarine containing 64.2 per cent of nonhydrogenated corn oil. During the 9-month study this diet was effective in achieving and maintaining a reduction of blood cholesterol levels. The diet raised the percentage of linoleic acid by about 300 per cent. The transition to the test diet went unnoticed by the majority of patients and by many members of the staff. A 13 per cent drop in serum cholesterol was found in 301 patients within 3 weeks. After 5 months the fall of cholesterol was about 23 per cent. The maximum change in weight was less than 1 Kg. during the test period. With resumption of usual diet, the serum cholesterol levels rose 19 per cent over a 3-month period. It was obvious that dietary alteration could be accomplished simply, easily, inconspicuously, and with an excellent degree of patient acceptability.

KITCHELL

Holman, R. L., McGill, H. C., Jr., Strong, J. P., and Greer, J. C.: Filtration Versus Local Formation of Lipids in Pathogenesis of Atherosclerosis. J.A.M.A. **170**: 416 (May 23), 1959.

The method whereby lipids accumulate in the inner layers of the arterial wall in atherosclerosis is one of the most cogent problems of our time. Evidence suggests that the active principles governing lipid transportation and local accumulations are enzyme-hormone complexes. The active metabolic work concerned is performed by the mesenchymal cells in the inner layers of the arterial wall. There are 3 stages leading to clinical disease: fatty streaking in the first 2 decades, conversion of some fatty streaks to fibrous plaques in the second 2 decades, and local complications such as hemorrhage and thrombosis about a plaque in the third 2 decades. Much confusion can be avoided by keeping interspecies differences in mind and recognizing the stage of atherosclerosis in man at any given age.

KITCHELL

Perkins, R., Wright, I. S., and Gatje, B. W.: Safflower Oil—Pyridoxine and Corn Oil—Pyridozine Emulsions. J.A.M.A. **169**: 1731 (April), 1959.

Serum cholesterol levels were studied in 22 healthy young men. An initial observation period of 5 weeks afforded a basis for forming 2 matched groups with equal mean serum cholesterol levels (221 mg. per 100 ml.). Thereafter 1 group received a supplement of safflower oil for 7 weeks. The other group received corn oil for 7 weeks followed by safflower oil for 7 weeks. A slight decrease was observed in average serum cholesterol level but was not found to be statistically significant. This study points out that if one wishes to lower significantly the serum cholesterol level, unsaturated fats should be used only when combined with a diet sharply limited in the use of saturated fats.

KITCHELL

BLOOD COAGULATION AND THROMBOEMBOLISM

Adams, C. W., and Hudgins, J. M.: Pulmonary Infarction after Dental Extraction. J.A.M.A. **170:** 412 (May 23), 1959.

Two case histories involving men aged 40 and 48 years illustrate the occurrence of pulmonary disease after extraction of teeth. Symptoms began 4 and 5 days after extraction, and the subsequent clinical course was marked by episodes of severe chest pain. Both patients recovered. These experiences suggest that the superior as well as the inferior venous circulation should be evaluated as the source of unexplained pulmonary infarction and one should distinguish between pulmonary embolism (arising from phlebothrombosis) and "virus pneumonia" after dental extraction.

KITCHELL

Koppel, J. L., Mueller, D. A., Novak, L. V., and Olwin, J. H.: Effects of Phosphoethanolamine and Phosphoserine on Blood Coagulation Mechanism. Am. J. Physiol. **196:** 1020 (May), 1959.

Phosphoethanolamine and phosphoserine can be converted to phosphatidyl ethanolamine and phosphatidyl serine respectively, by the action of certain phospholipase D preparations and by cytidine coenzymes. Phosphatidyl ethanolamine has been shown under certain conditions to have clot-promoting properties, whereas phosphatidyl serine has clot-inhibiting activity. Both phosphoethanolamine and phosphoserine have marked anticoagulant properties when added to freshly drawn, normal human blood. When added to normal human plasma in the presence of either brain extract thromboplastins or Russell viper venom they produced an inhibition of clot formation that became more pronounced with increasing concentration. The effects appeared to be due to an interference with thrombin formation rather than to an inhibition of the thrombin-fibrinogen reaction. It was suggested that, depending upon their concentration, phosphoethanolamine and phosphoserine may inhibit either the formation of a prothrombin-converting principle only or inhibit, in addition, the activity of this principle as well.

KAYDEN

Shoulders, H. H., Jr., Hartmann, R. C., and Meng, H. C.: Effects of Intravenous Administration of a Fat Emulsion on Blood Coagulation in Dogs. Am. J. Physiol. **196:** 1015 (May), 1959.

A fat emulsion was prepared from cottonseed oil, soybean phosphatides, and synthetic emulsifying agents and given intravenously to dogs. During the infusions the animals developed thrombocytopenia and shortened clotting times. When additional infusions were given within 3 hours, no significant changes were noted. If the time interval was extended to from 1 to 13 days, variable responses occurred, including at times, hypercoagulability. If the time interval after the first infusion was extended to beyond 2 weeks after the initial infusion, the effects were similar to those observed during the first infusion. The prothrombin and thrombin clotting times and plasma fibrinogen concentration were not greatly altered during the infusion. Abnormal bleeding time, prothrombin utilization, and clot retraction accompanied the thrombocytopenia.

KAYDEN

Swank, R. L.: Changes in Blood of Dogs and Rabbits by High Fat Intake. Am. J. Physiol. **196:** 473 (Mar.), 1959.

The effect of large butterfat meals on the blood of rabbits and dogs was studied. Marked distortions of the red blood cells occurred with aggregation, despite no elevation in blood viscosity. The circulation time was prolonged, and a decrease in plasma surface tension was observed hours after the butterfat meal. The platelet count was unchanged in the rabbit, but was markedly decreased in the dog. The leukocyte count was unchanged in the rabbit, but increased in the dog after an initial fall. The erythrocyte sedimentation rate was usually decreased in both species. The clotting time was also usually decreased after butterfat meals, and the clots that were formed were gelatinous and friable. Most animals showed changes in the buffy coat consisting in a thinning of the coat, or a change in color to pink or red without any change in size. The latter effect was due to intimate mixing of the red blood cells with platelets and leukocytes. Some of these changes are noted in human subjects after fat meals.

KAYDEN

CONGENITAL ANOMALIES

Blount, S. G., Jr., Vigoda, P. S., and Swan, H.: Isolated Infundibular Stenosis. Am. Heart J. **257:** 684 (May), 1959.

Three documented cases of infundibular stenosis are presented and discussed. This lesion was found in 3 per cent of all cases of pulmonary stenosis with intact ventricular septum. On auscultation infundibular stenosis may be separated from pulmonary stenosis because the murmur and thrill are of maximum intensity in the second to third intercostal spaces parasternally, or lower, and the murmur is always louder in the third left intercostal space than in the first left intercostal space. When an infundibular-chamber pressure curve can be

demonstrated on cardiac catheterization the diagnosis is clear cut. It should be suspected when a transition zone between the pulmonary arterial pressure curve and the right ventricular curve is found at a point much below the usual site of the pulmonary valve. Surgical correction of the lesion was performed in the 3 patients under hypothermia. In 2 patients the pressure gradient was completely abolished and in the third it was halved. Symptomatically all 3 patients were improved.

SAGALL

Braudo, J. L., and Zion, M. M.: The Cyanotic (Syncopal) Attack in Fallot's Tetralogy. Brit. M. J. 1: 1323 (May 23), 1959.

A 2¼-year-old patient with "acyanotic Fallot's tetralogy" developed a cyanotic (syncopal) attack during right heart catheterization. The attack was probably caused by the prolonged presence of the catheter in the pulmonary outflow tract. During the syncope, hemodynamic data were obtained that supported the postulation by Wood that these attacks were probably due to increased resistance to the flow of blood through the narrow infundibulum. This in turn caused increased shunting of blood from right ventricle into the aorta and a fall in arterial oxygen saturation. Procaine administered intravenously was partially successful in treating the attack. However, sustained improvement was obtained only after the use of morphine.

KRAUSE

Downing, D. F.: Cardiac Catheterization in Congenital Heart Disease. J.A.M.A. 170: 770 (June 13), 1959.

The author presents the results of 2,000 cardiac catheterizations performed personally and analyzed with respect to the various technics, risks, and value gained from the procedures. The view that cardiac catheterization is dangerous should take into account the fact that these patients were examined in all stages of decompensation and many were in severe distress. In this large series only 1 death was attributed to the procedure. Definitive treatment of congenital heart disease is surgical and information obtained by cardiac catheterization will reduce the number of patients operated upon for incurable defects or denied operation for defects that could be corrected.

KITCHELL

Lev, M.: The Architecture of the Conduction System in Congenital Heart Disease. II. Tetralogy of Fallot. Arch. Path. 67: 572 (May), 1959.

Four hearts with tetralogy of Fallot were dissected and studied grossly and histopathologically. Each specimen showed mild abnormalities related to the position of the aorta and the topography of the right ventricle. The course of the atrioventricular (AV) node, bundle, and bundle branches was described. The altered embryogenesis of these was discussed, and various theories of the cause of the anomaly were briefly reviewed. The architecture of the conduction system in tetralogy of Fallot was altered thus: the A-V bundle was on the left side of the summit of the ventricular septum, below the ventricular septal defect, the right bundle branch was on occasion divided into 2 or more parts, the left bundle branch might be more compact, with anterior and posterior divisions occurring further down in the septum, the right bundle branch was adjacent to and might be involved in, any fibroelastosis appearing in the conus, and the A-V node might be deviated horizontally if a left superior vena cava enters the coronary sinus.

MAXWELL

Ellis, K., Leeds, N. E., and Mimmelstein, A.: Congenital Deficiencies in the Parietal Pericardium; A Review with Two New Cases Including Successful Diagnosis by Plain Roentgenography. Am. J. Roentgenol. 82: 125 (July), 1959.

Congenital pericardial deficiency, described first in 1559, is a rare anomaly that has seldom been diagnosed prior to death. The 2 patients presented herein represent the ninety-eighth and ninety-ninth reported in the literature. They both had left-sided pericardial deficiencies, which were the commonest type of lesion noted. Roentgen findings included a shift of the heart to the left, and an unusual cardiac silhouette in the frontal projection where the left heart border was flattened as the heart stretched out over the left diaphragm dome. Three convexities were seen along the left heart border: the aortic knob; a long, prominent, and sharply demarcated pulmonary artery segment; and a distinct left ventricle segment. Confirmation of suspected lesions could be had by the use of diagnostic pneumothorax. Cardiac fluoroscopy, angiocardiography, and cardiac catheterization were not particularly useful in the diagnosis.

KITCHELL

Hahn, C., and Risch, F.: Considerations on the Closure of the Interatrial Defects under Hypothermia in 90 Cases. Cardiologia 34: 265, 1959.

Observations made in 90 patients with atrial septal defect (with and without anomalies of pulmonary veins) operated upon under hypothermia are reported. Among the patients with uncomplicated atrial septal defect the mortality was 1.5 per cent, whereas the over-all mortality was 5.5

er cent. All fatalities occurred among the first 0 patients. Follow-up a few months after operation in the first 56 patients, including 13 catheterizations, demonstrated that the defect had been closed. The advantages of the authors' method, as compared with that of others, are discussed.

BRACHFELD

Robinson, G., Glotzer, P., Gilbert, M., Escher, D. J. W., and Hurwitt, E. S.: Interventricular Septal Defects with Associated Major Vascular Anomalies. Report of Three Cases. Am. J. Cardiol. 3: 746 (June), 1959.

Three children, each having a ventricular septal defect plus one or more great vessel anomalies, are briefly described and the surgical treatment of multiple lesions is discussed. Prior division of a patent ductus arteriosus reduces blood loss from the heart when it is opened for repair of the septal defect. Excision of an aortic coarctation lessened the shunting through the septal defect and thereby could make its closure better tolerated. In artificial circulatory maintenance via the femoral artery, perfusion of the head area was facilitated by prior correction of the coarctation. Anomalous pulmonary veins could be corrected before or after the closure of the septal defect, since they did not interefere with circulatory bypass.

ROGERS

Toscano-Barboza, E. and DuShane, J. W.: Ventricular Septal Defect. Correlation of Electrocardiographic and Hemodynamic Findings in 60 Proved Cases. Am. J. Cardiol. 3: 721 (June), 1959.

Detailed analysis of the electrocardiogram was correlated with hemodynamic and anatomic findings in 57 patients undergoing open cardiotomy for ventricular septal defect and in 3 similar cases examined post mortem. The resulting data formed into 3 groups. Group I consisted of 20 patients presenting principally diastolic overloading of the right ventricle indicated by: RSR′, RsR′, rsR′ patterns in V_1; electrical QRS axis usually rightward of +120 degrees; delay of the intrinsicoid deflection in V_1; evidence of increased right ventricular blood flow anatomically and by cardiac catheterization in 17 patients. Group II consisted of 10 patients who showed mainly diastolic overloading of the left ventricle (heightened left precordial R and T waves, delay in the intrinsicoid deflection in V_5 and a tendency to counterclockwise rotation of the QRS axis) or right ventricular systolic overloading associated with increased pulmonary arteriolar resistance (rR′s or rR′ in V_1 with normal intrinsicoid deflection delay in V_1). In all 10 patients the septal defect was located in the outflow tract of the right ventricle where the shunt was unlikely to impose diastolic overloading of the right ventricle. Group III consisted of 30 patients presenting mixtures of features described for groups I and II.

ROGERS

Warren, J. E., and Jannicelli, A. L.: Reassessment of Electrocardiographic Findings in Isolated Interventricular Septal Defect. Am. J. Cardiol. 3: 733 (June), 1959.

The electrocardiograms of 51 patients having an isolated ventricular septal defect were studied. Right or left axis deviation was found in 27 per cent. P-wave abnormalities were noted in 16 per cent. Right bundle-branch block was incomplete in 20 per cent, complete in 2 per cent; left bundle-branch block was not encountered. Ventricular hypertrophy appeared to be predominantly right in 12 per cent, left in 10 per cent and was combined in 20 per cent. The findings varied in different age groups.

ROGERS

CONGESTIVE HEART FAILURE

Donald, K. W.: Hemodynamics in Chronic Congestive Heart Failure. J. Chron. Dis. 9: 476 (May), 1959.

The author discusses mainly pressure and flow in various states. The first hemodynamic stage of ventricular failure is a rise of ventricular diastolic end filling pressure, usually without a reduction in output until later. The term "congestive failure" is used here when evidence of abnormal filling pressures appear during any normal degree of activity, not just at rest. Early, less familiar, causes and events are stressed. In right ventricular failure, the myocardium may fail without any added pressure or flow load, as in coronary artery disease or a toxic myocarditis. The largest group is myocardial failure with excessive load. Then even minimal coronary artery or metabolic disease can be critical. The commonest cause of overloading is pulmonary hypertension caused by mitral stenosis. Increased pulmonary vascular resistance may be due in part to negative intrathoracic pressure, variations in compliance between different areas of the lungs, or degenerative endothelial changes and their vasomotor effects. Whatever the causes, this increased pulmonary vascular resistance is the most important factor in the development of right ventricular failure. The close correlation between the degree of pulmonary vascular resistance, the exercising cardiac output response, and the resting cardiac output lends support to the hypothesis that the onset of right ventricular

insufficiency on exercise may be the initiating factor. An acute respiratory infection in patients with pulmonary emphysema may produce near-lethal hypoxemia, but recovery is often remarkable with antibiotics, oxygen, and digitalis. Causes of increased work and excessive load are discussed, as are other factors influencing cardiac output and the circulation in other parts of the body.

MAXWELL

Guyton, A. C.: The Systemic Venous System in Cardiac Failure. J. Chron. Dis. 9: 465 (May), 1959.

In acute cardiac failure, the sympathetic nervous system greatly increases venomotor tone within seconds, causing not constriction of veins, but a tightening of their walls, with an increase in pressure everywhere in the venous system except where the veins empty into the heart. The elevated venous pressure gradient helped to maintain adequate cardiac output by increasing the blood supply to the damaged heart. Other factors that compensated for elevated right atrial pressure were an increase of mean capillary pressure, caused by retention of fluid in the tissues, and the plasticity of the veins, which permitted them to distend to as much as twice their normal volume, with resulting decrease in venous resistance. This effect also increased the return of blood to the heart and cardiac output. Experimental animals with intact sympathetic reflexes could withstand far more cardiac weakness than could those without intact reflex pathways. A rise in capillary pressure began after fluid retained by the kidneys had operated to raise venous pressure still higher and to diminish the reflex constriction of the arterioles that occurred in the acute stage. Very high capillary pressure resulted in edema. If the compensating factors did not return cardiac output to near normal, renal retention of fluid might continue, with increasing edema. The heart finally deteriorated, apparently because of too much input pressure and perhaps also diminished nutrition as a result of edema within the heart musculature. Treatment that prevented continued fluid retention often also prevented cardiac deterioration.

MAXWELL

Hejtmancik, M. R., Herrmann, G. R., Kroetz, F. W.: The Effects of SU-5879 (Esidrix) in Congestive Heart Failure and Hypertension: A Clinical Evaluation. Am. Heart J. 57: 490 (Apr.), 1959.

In a study of 19 hospitalized and 17 ambulatory patients in congestive heart failure SU-5879 (Hydrochlorothiazide, Ciba) was found to be an effective diuretic agent of low toxicity with a diuretic action similar to that of the mercurials and chlorothiazide. A single oral dose of 200 mg. in about 2 hours resulted in a conspicuous diuresis, which persisted for over 24 hours. Effective diuresis also was achieved by 50-mg. doses given twice daily. Administration of the drug resulted in an increased urinary excretion of sodium and chloride with a decrease in serum chloride levels and an increase of serum carbon dioxide. There was a moderate increase in potassium excretion and, in a few patients, levels of serum potassium below 4.0 mEq./L. appeared after 1 week of therapy. One ambulatory patient actually developed clinical symptoms of hypopotassemia, which abated on discontinuance of the drug and the administration of oral potassium. In some patients slight elevation in blood urea nitrogen was observed, but none developed serious renal insufficiency. In 18 of 26 hypertensive patients significant reductions of blood pressure occurred. No serious complications referrable to the drug developed in this series. However, the low serum potassium levels found in a few patients and the occasional moderate rise in blood urea nitrogen indicate caution in long-term therapy.

SAGALL

Taquini, A. C.: Right Ventricular Failure. Acta Cardiol. 14: 101, 1959.

Hemodynamic changes common to all the different forms of right ventricular failure are increased end-diastolic filling pressure of the right ventricle, right atrial pressure, effective venous pressure, and increased blood volume. Work carried out on patients and in laboratory animals tended to show that the ventricle follows Starling's law. The effective cardiac output was found to be low in all instances. If the resistance surpassed a critical limit, the right ventricle failed to maintain an output adequate to the demands and this in turn gave rise to a collapse and further fall of cardiac output. Hemodynamically the increased blood volume had 2 roles. First, it filled the venous system with a consequent increase in the effective venous pressure, a condition necessary for the maintenance of a pressure gradient when the diastolic pressure of the ventricle and the atrial pressure increased. Second, it limited the modifications of the venous return to the heart produced by changes in position. The increased blood volume allowed the venous circulation to adapt itself to the altered circulatory dynamics imposed by the failing ventricle. As in normal conditions the venous circulation adapted itself to changes in blood distribution by means of reflex mechanisms that produced venous constriction or dilatation, with a difference

that it did so at higher effective pressures. The greater the venous distension the higher was the effective venous pressure and the lesser was the role played by the venomotor changes in the ventricular filling. In organic tricuspid lesions the flow and reflux showed a linear correlation both at rest and during exercise, which discarded the theory that the fall in cardiac output in these patients was due to an isolated increase in the amount of blood regurgitated.

BRACHFELD

Turino, G. M., and Fishman, A. P.: The Congested Lung. J. Chron. Dis. **9:** 510 (May), 1959.

The anatomic, physiologic, and clinical abnormalities of the lung in the presence of vascular engorgement and anatomic changes in the lung resulting from pulmonary venous hypertension are discussed. Patients adopted a pattern of rapid breathing, with small tidal volume, a device that minimizes the work of breathing through unknown mechanisms. Hyperventilation also helped to decrease the energy cost of breathing by raising alveolar oxygen tensions and lowering carbon dioxide tensions. In this way, inspired air and blood were better distributed. Treatment of acute congestion included the upright position to curtail blood flow into the lungs, venous occlusion tourniquets or phlebotomy, and positive-pressure breathing. Cardiotonic agents were used for left-sided heart failure and surgical treatment for mitral stenosis. In chronic congestion, treatment was directed toward the control of edema and the prevention of sudden increases in venous return through too strenuous exercises.

MAXWELL

Soloff, L. A., and Zatuchni, J.: Clinical Experiences with Digoxin. Am. Heart J. **257:** 674 (May), 1959.

A clinical study of digoxin indicated that the drug was a safe, effective and versatile digitalis preparation for oral, intramuscular, and intravenous use. The safe initial digitalizing dose was found to be either 2 mg. orally or 1.5 mg. intravenously or intramuscularly. In the presence of actual or suspected acute myocardial infarction one half of that dose should be employed. For those patients previously well maintained who developed acute congestive heart failure because of some precipitating event an intramuscular dose of 0.75 mg. was safe and usually effective. About 2 hours after the initial dose a maintenance regimen of 0.25 to 0.75 mg. was used with individualization of dosage for each patient depending on the fall in ventricular rate and the production of nausea, which almost always was the initial manifestation of toxicity. The intramuscular maintenance dose was identical to the oral dose and could be substituted without any noticeable change in the effectiveness of the drug.

SAGALL

CORONARY ARTERY DISEASE

Broch, O. J., Humerfelt, S., Haarstad, J., and Myhre, J. R.: Hemodynamic Studies in Acute Myocardial Infarction. Am. Heart J. **57:** 522 (April), 1959.

In 35 patients with acute myocardial infarction hemodynamic determinations with the dye-dilution technic disclosed normal circulatory conditions in the 18 mild or moderately severe cases and a marked reduction of the cardiac output and the stroke volume with a prolonged appearance and passage time in the 17 severe cases. Reexamination 3 weeks later showed no significant differences in the 18 mild or moderately severe cases and a definite trend toward normal in the 9 survivors among the 17 severe cases. A comparison of the various categories of cases on admission revealed small differences only in the values for total blood volume and intrathoracic blood volume, with small changes in the values between the first and second examinations.

SAGALL

Cobb, L. A., Thomas G. I., Dillard, D. H., Merendino, K. A., and Bruce, R. A.: An Evaluation of Internal-Mammary-Artery Ligation by a Double-Blind Technic. New England J. Med. **260:** 1115 (May 28), 1959.

A double-blind technic was employed to study the effects of ligation of the internal mammary artery on patients with angina pectoris. Of the 17 patients with serious angina who were investigated, 8 had their internal mammary arteries ligated and 9 underwent the operative procedure, but did not have the arteries ligated. The patients were followed postoperatively for 3 to 15 months. During the first 6 months, 5 out of 8 of the ligated patients and 5 out of 9 of the nonligated patients reported significant subjective improvement. Improvement in exercise tolerance, however, was found in only 2 patients, both of whom had not been subjected to ligation. It was concluded on the basis of this study that ligation of the internal mammary artery had no effect on the pathophysiology of coronary artery disease and that the subjective benefit reported from this operation most likely was on a psychologic basis or due to a spontaneous unrelated improvement in collateral circulation.

SAGALL

Freundlich, J., and Sereno, L. R.: Auricular Infarction. Am. Heart J. **257:** 654 (May), 1959.

Two cases of atrial infarction with postmortem confirmation are presented. In 1 patient the infarction was diagnosed electrocardiographically before death on the basis of an abnormal form of the P wave. The diagnosis of atrial infarction is usually based on a disturbed atrial mechanism, deviation of the P-T_a segment, and abnormal shape of the P wave. In a patient with an acute coronary occlusion, changes in the atrial complex of the electrocardiogram constitute strong evidence for an acute atrial lesion. SAGALL

Haeger, K., and Wallgren, G. R.: Studies of the Coronary Circulation. IV. Surgical Treatment of Acute Experimental Myocardial Infarction in the Dog. J. Thoracic Surg. **37:** 545 (April), 1959.

Attempts to decrease the mortality after myocardial infarction by excising the area of infarction have been attended with a high operative mortality. Recently coronary occlusion has been simulated in the dog by the insertion of a magnesium-aluminum alloy needle in 1 of the major coronary arteries. In these experiments an 18- to 23-mm. piece of alloy was inserted into the lumen of the right coronary artery proximal to its main bifurcation, into the left descending without interference with the septal branch, or into the left circumflex branch just distal to the main bifurcation of the left common coronary artery. In 16 dogs subjected to this procedure all died within 15 days of the operation. Eleven of this group could be considered as having had a gradual coronary occlusion due to obstruction of the lumen by either the needle or the thrombus formation. In another 15 dogs a Nylon tube 2.4 to 2.8 mm. in external diameter was inserted into the internal mammary artery and the distal end pushed through the epicardium at the zone between the infarcted and healthy myocardium and held in place by a black silk-purse-string suture. This was done in a second operation when the dogs began to show electrocardiographic signs of myocardial ischemia or the condition of the dog became alarming. In this group 11 dogs survived, the time of observation being at least 4 months. Two dogs who died from pulmonary complications were found to have patent tubes. One dog died 15 days after the second operation; in this animal the tube was patent and the myocardium was in the healing stage of infarction. One dog died of ventricular fibrillation as soon as the chest was closed. In 6 dogs the Nylon tube was inserted but closed. All these dogs died shortly after the second operation. The longest survival was 6 days in this group and 10 days in the original control group. The Nylon tubes were inserted at the border between the infarcted and normal zones because the sutures held better and this border zone has been shown to be the site of ectopic foci that may lead to ventricular fibrillation. It would certainly appear that implantation of the Nylon-tube anastomosis of the internal mammary artery into the myocardium is effective in reducing the mortality of experimental coronary occlusion in the dog. LEVINSON

Haeger, K., and Wallgren, G. R.: Studies of the Coronary Circulation. III. Intramyocardial Implantation of Nylon Tubes after Ligation of a Major Coronary Artery. J. Thoracic Surg. **37:** 532 (April), 1959.

The Vineberg technic of implanting the internal mammary artery into the left myocardium has not been too successful because the vessels very often are obliterated by endarteritic changes and thrombus formation. Since polyethylene or Nylon tubes frequently remained patent when inserted into coronary arteries, it seemed feasible to use these tubes as a bridge between the internal mammary artery and the ischemic myocardium. With ligation of the right coronary artery the mortality was 93 per cent. Ligation of the left descending coronary artery, avoiding the septal branch, resulted in 100 per cent mortality in 7 dogs. After unilateral implantation of the Nylon tube, ligation of a major coronary artery resulted in a mortality of only 2 out of 12 dogs in this series, so that it added to the protection of the heart. Nylon tubes implanted into the myocardium invariably became occluded by thrombosis after 6 weeks, which was believed to be a sufficient length of time to permit development of the coronary anastomoses as functional units. It was shown by implantation of the tubes in such organs as the liver, spleen and striated muscle that occlusion of the vessel occurred in all but 2 of 20 animals in from 5 to 14 days after insertion. Difference in velocity of blood flow to the myocardium, better venous return to the heart, and differences in vasomotor innervation of the coronary system were offered as explanations for the lesser tendency to thrombus formation in the coronary vessels. Variations in biochemical factors occurring in the ischemic myocardium were also discussed as possible factors in this difference in thrombus formation. In the technic of inserting the tubes it was found that hematomas occurred less frequently when the end of the Nylon tube was kept closed and several needle perforations were made in the tube. The end of the tube was shaped to a sharp point. When the patent Nylon tube was clamped the animal usually died of myocardial infarction. LEVINSON

Prevention of Rheumatic Fever and Bacterial Endocarditis Through Control of Streptococcal Infections*

Rheumatic fever is a recurrent disease which frequently can be prevented. Infection with group A streptococci precipitates both initial and recurrent attacks; therefore, prevention of rheumatic fever and rheumatic heart disease depends upon the control of streptococcal infections. This may be accomplished, one by prevention of streptococcal infections in *rheumatic* subjects, and, two by early and adequate treatment of streptococcal infections in *all* individuals.

Bacterial endocarditis may result from dental and other surgical procedures in patients with rheumatic or congenital heart disease. When such procedures are undertaken, these patients should be protected by *administration of antibiotics in therapeutic doses.*

I. Prevention of Recurrences in Rheumatic Individuals

A. Continuous Prophylaxis

Many streptococcal infections occur without producing clinical manifestations. For this reason, prevention of recurrent rheumatic fever must depend on continuous prophylaxis rather than solely on recognition and treatment of acute attacks of streptococcal disease.

General Recommendations

Who should be given prophylaxis?

In general, all patients who have a *well documented history* of rheumatic fever or chorea, or who show *definite evidence* of rheumatic heart disease, should be given continuous prophylaxis.

Although recurrent attacks of rheumatic fever occur at any age, the risk of recurrences decreases with the passage of years. Some physicians may wish to make exceptions to instituting or maintaining prophylaxis in certain of their adult patients, particularly those without heart disease who have had no rheumatic attacks for many years.

How long should prophylaxis be continued?

The risk of acquiring a streptococcal infection and the possibility of rheumatic fever recurrences continue throughout life. It is, therefore, suggested that the safest general procedure is to continue prophylaxis indefinitely, particularly if rheumatic heart disease is present.

When should prophylactic treatment be initiated?

Active rheumatic fever: Prophylaxis should be initiated as soon as the diagnosis of rheumatic fever is made, or any time thereafter when the patient is first seen. The streptococcus should be eradicated with penicillin (see Treatment Schedules p. 153), and following this the prophylactic regimen should be instituted.

Inactive rheumatic fever: In inactive rheumatic fever, prophylaxis should be instituted when the patient is first seen.

Should prophylaxis be continued during the summer?

Yes, continuously. Streptococcal infections can occur at any season, although they are more prevalent in the winter.

Specific Prophylactic Methods

Several effective methods of continuous prophylaxis are available, and the physician must decide which is most suitable for an individual patient.

Oral vs. intramuscular route—Oral medication depends on patient cooperation. Most failures occur in patients who fail to ingest the drug regularly. Patients should receive careful and repeated instructions on this point from the physician. Patients who have proved unreliable in taking oral medication should receive long-acting depot penicillin, given intramuscularly once a month.

Penicillin vs. sulfonamides—Sulfadiazine has the advantage of being easy to administer, inexpensive, and effective. Although resistant streptococci have appeared during mass prophylaxis in the armed forces, this is rare in civilian populations.

Penicillin rarely produces serious toxic reactions. It has the further advantage of being bactericidal for group A streptococci, and strains of group A streptococci resistant to penicillin have not been encountered.

1. BENZATHINE PENICILLIN G—INTRAMUSCULAR

Dosage—1,200,000 units once a month.

Toxic reactions

Urticaria and angioneurotic edema

*This statement was prepared by the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis appointed by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association. The committee is cognizant of the fact that no recommendations of any group can be final at this time. The present approach may not be the eventual solution of the problem of preventing rheumatic fever. Revisions and changes will be made as new knowledge may indicate.

Reactions similar to serum sickness include fever and joint pains and may be mistaken for rheumatic fever.

Some discomfort due to local irritation at the injection site is usual.

A careful history of allergic reactions to penicillin should be obtained. Although many individuals who have had reactions to penicillin may subsequently be able to tolerate the drug, it is safer not to use penicillin if the reaction has been severe and particularly if angioneurotic edema has occurred.

2. SULFADIAZINE—ORAL

Dosage—from 0.5 to 1.0 Gm., once a day. The smaller dose is to be used in children under 60 pounds.

Toxic reactions are infrequent and usually minor. In any patient being given sulfonamides, consider all rashes and sore throats as possible toxic reactions, especially if they occur in the first eight weeks. In patients on this prophylactic regimen, it is hazardous to treat toxic reactions or intercurrent infections with sulfonamides.

The Chief Toxic Reactions are:

Skin eruptions

Morbilliform—continue drug with caution. Urticaria or scarlatiniform rash associated with sore throat or fever—discontinue drug.

Leukopenia

Discontinue drug if white blood count falls below 4,000 and polynuclear neutrophils fall below 35% because of possible agranulocytosis which is often associated with sore throat and a rash. Because of these reactions, weekly white blood counts are advisable for the first two months of prophylaxis. The occurrence of agranulocytosis after eight weeks of continuous prophylaxis with sulfonamides is extremely rare.

3. PENICILLIN—ORAL

Dosage—200,000 to 250,000 units once or twice a day. Twice daily is probably more effective.

Toxic reactions—except for local irritation, reactions are similar to those with intramuscular penicillin, but occur less frequently and tend to be less severe. A careful history concerning penicillin allergy should, however, be obtained.

B. Treatment of Streptococcal Infections in Rheumatic Individuals

When streptococcal infections occur despite a prophylactic regimen, or occur in a rheumatic subject who is not receiving continuous prophylaxis, they should be treated promptly and vigorously. At least the maximal dose regimen recommended for treatment of streptococcal infections in the general population (Section II, p. 153) should be employed. Despite optimal therapy, it is sometimes not possible to prevent rheumatic recurrences once streptococcal infections occur in the rheumatic subject.

C. Protection of Rheumatic Fever Patients in Hospital Wards

Patients with rheumatic fever or rheumatic heart disease are often exposed to increased hazards in hospital wards as the result of contact with streptococcal carriers or patients with active streptococcal infections.

Patients with inactive rheumatic fever or rheumatic heart disease should be placed on continuous streptococcal prophylaxis on admission to the hospital or as soon thereafter as the diagnosis is established. (See Section IA, "Continuous Prophylaxis.") If oral penicillin is used, a dosage of 200,000 to 250,000 units *twice a day* is preferable.

Patients with acute rheumatic fever should be treated first with therapeutic doses of penicillin to eradicate streptococci. (See "General Recommendations—When should prophylactic treatment be initiated?" Section I, and "Recommended Treatment Schedules," Section II.)

II. Treatment of Streptococcal Infections in the General Population

During epidemics, and in certain population groups, it has been found that about 3% of untreated streptococcal infections are followed by rheumatic fever. Adequate and early penicillin treatment, however, will eliminate streptococci from the throat and prevent most attacks of rheumatic fever.

A. Diagnosis of Streptococcal Infections

The accurate recognition of individual streptococcal infections, their adequate treatment, and the control of epidemics in the community presently offer the first practical means of preventing initial attacks of rheumatic fever.

About half of the streptococcal infections which occur are likely to escape detection because they are asymptomatic or atypical. The other half can often be suspected by their clinical manifestations. However, in the absence of a scarlatinal rash, it is impossible to differentiate streptococcal infections with certainty on clinical grounds alone. Therefore, *bacteriological support (by throat culture) of the clinical impression is highly desirable.* The following section on diagnosis has been included in order to assist physicians in making a correct diagnosis and assuring adequate treatment.

1. SYMPTOMS

Sore throat—sudden onset, pain on swallowing
Headache—common

Fever—variable, but generally from 101° to 104° F.

Abdominal pain—more common in children than in adults

Nausea and vomiting—common, especially in children

2. SIGNS

Red throat

Exudate—usually present

Lymphadenopathy—swollen, *tender* lymph nodes at angle of jaw

Rash—scarlatiniform, when present, usually diagnostic of a streptococcal infection

Acute otitis media, Acute sinusitis } frequently due to the streptococcus

In the absence of the above symptoms and signs, occurrence of any of the following symptoms is usually not associated with a streptococcal infection: simple coryza, hoarseness, cough.

3. LABORATORY FINDINGS

Throat culture*—hemolytic streptococci are almost invariably recovered on culture during acute streptococcal infections. A single well-done culture is usually sufficient, although hemolytic streptococci which are occasionally missed on initial culture may be detected in subsequent cultures.

White blood count—generally over 12,000.

B. Treatment of Streptococcal Infections

Treatment should be started as soon as possible, but the 18 to 24 hour delay entailed in making a diagnosis by awaiting the results of a throat culture does *not* reduce the efficacy of antibiotic treatment in preventing the occurrence of rheumatic fever.

Penicillin is the drug of choice. Effective blood levels should be maintained for *a period of 10 days* to prevent rheumatic fever by eradicating the streptococci from the throat. Even with this prolonged treatment, streptococci may sometimes fail to be eradicated, especially when oral therapy is used. If possible, a follow-up culture two days after discontinuing treatment is desirable to ascertain the absence of hemolytic streptococci.

Penicillin may be administered by either intramuscular or oral route. Intramuscular administration is recommended as the method of choice since it ensures adequate blood levels for a sufficient length of time. Oral therapy, by contrast, is dependent upon the cooperation of the patient.

Recommended Treatment Schedules

1. INTRAMUSCULAR PENICILLIN

Benzathine penicillin G:

Children—one intramuscular injection of 600,000 to 900,000 units. (The larger dose is probably preferable for children over 10 years of age.)

Adults—one intramuscular injection of 900,000 to 1,200,000 units.

OR

Procaine penicillin with aluminum monostearate in oil:

Children—one intramuscular injection of 300,000 units, every third day for 3 doses.

Adults—one intramuscular injection of 600,000, every third day for 3 doses.

2. ORAL PENICILLIN

Children and adults—200,000 to 250,000 units, three times a day for a *full 10 days*. Therapy must be continued *for the entire 10 days* even though the temperature returns to normal and the patient is asymptomatic.

3. OTHER ANTIBIOTICS

Broad-spectrum antibiotics, such as erythromycin and the tetracyclines are useful in patients who are sensitive to penicillin. If given *for 10 days*, these antibiotics are possibly as effective as *oral* penicillin in the treatment of streptococcal infections, but are subject to the same uncertainties of administration by the oral route.

CAUTION!

The sulfonamide drugs should *not* be used for the *treatment* of streptococcal infections. In an established infection, they will not eradicate the streptococcus and therefore will not prevent rheumatic fever. However, the sulfonamides *are effective* in preventing reinfection and recurrences when administered as *continuous prophylaxis* to rheumatic subjects. (See "Specific Prophylactic Methods," Section I.)

Antibiotic troches and lozenges are also inadequate for the treatment of streptococcal infections because they do not eliminate the streptococcus.

III. Prophylaxis against Bacterial Endocarditis

In individuals with rheumatic or congenital heart disease, bacteria may lodge on the heart valves or other parts of the endocardium, producing bacterial endocarditis.

Although transient bacteremia is a rather common phenomenon and may occur after the mere chewing of hard candy or brushing of teeth, it is likely that the number of organisms entering the blood stream is usually relatively low under such

*"A Method for Culturing Beta-Hemolytic Streptococci from the Throat" may be obtained from your Heart Association or from the American Heart Association. This outline is based on the chapter on streptococci by Armine T. Wilson, M.D., 4th Edition of Diagnostic Procedures and Reagents, to be published by the American Public Health Association.

circumstances. Transient bacteremia is especially apt to occur after dental extraction or other procedures in which the gums are manipulated, after removal of the tonsils and adenoids, and as a consequence of genitourinary operative procedures such as catheterization or cystoscopy. It is also probable that delivery is associated with transient bacteremia.

Since patients with rheumatic or congenital heart disease are especially vulnerable to bacterial endocarditis, it is advisable to protect such patients with antimicrobial agents when they are to be subjected to any of the above procedures. Some cardiologists are of the opinion that these patients should also receive prophylaxis against bacterial endocarditis when subjected to any surgery involving general anesthesia, or to diagnostic procedures such as cardiac catheterization.

General Recommendations for Dental Manipulations and Oral Surgery

Penicillin is the drug of choice for administration to patients with rheumatic or congenital heart disease undergoing dental manipulations or surgical procedures in the oral cavity.

Although the exact dosage and duration of therapy are empirical, there is some evidence that for effective prophylaxis, reasonably high concentrations of penicillin must be present at the time of these procedures. *The dosage regimens employed for long-term prophylaxis against Group A streptococci in rheumatic susceptibles are inadequate for preventing bacterial endocarditis.* To prevent organisms from lodging in the heart valves or to eradicate them promptly before the formation of a vegetation, high levels of penicillin in the blood over a period of several days after the given procedure are recommended.

Extraction of teeth from badly infected gums is apt to result in more intense bacteremia than when infection is minimal or absent. If prophylaxis is instituted 24 to 48 hours prior to the operative procedure, it may decrease the intensity of bacteremia. Since occult infection may be present, some workers recommend that treatment always be started several days prior to the operative procedure. On the other hand, some workers have been concerned that pretreatment might lead to the emergence of antibiotic-resistant microorganisms. These would constitute a very difficult therapeutic problem if they implanted in the valves. It has, therefore, been argued that prophylaxis should not be instituted until immediately before the operative procedure.

In view of the lack of definitive evidence to support categorically either method, the physician must evaluate the likelihood of infection and decide whether a period of preliminary treatment prior to the operative procedure is indicated. It is emphasized that there is *no disagreement* regarding the advisability of using antimicrobial agents immediately before and subsequent to the operative procedure.

Suggested Treatment Schedules

Two regimens are presented. In one, the intramuscular route is used throughout. In the other, oral therapy is combined with a single injection of penicillin one hour prior to the surgical procedure. Because of practical considerations some physicians and dentists rely on oral penicillin alone when the full cooperation of the patient is assured. It should be emphasized that these regimens are only empirical guides.

Intramuscular Regimen:

Step I.* Prophylaxis extended to two day period before surgery:

600,000 units of procaine penicillin I.M. on each day.

Step II. Day of surgery:

600,000 units procaine penicillin I.M. supplemented by 600,000 units of crystalline penicillin I.M., one hour before surgical procedure.

Step III. For two days after surgery:

600,000 units procaine penicillin I.M. each day.

Intramuscular Plus Oral Regimen:

Step I.* Prophylaxis extended to two day period before surgery:

500,000 units of buffered penicillin G or phenoxymethyl penicillin (penicillin V), by mouth four times a day.

Step II. Day of surgery:

500,000 units of buffered penicillin G or phenoxymethyl penicillin (penicillin V), by mouth four times a day, supplemented by 600,000 units crystalline penicillin I.M. one hour before surgical procedure.

Step III. For two days after surgery:

500,000 units of buffered penicillin G or phenoxymethyl penicillin (penicillin V), by mouth four times a day.

Contraindications to above regimens:

Sensitivity to penicillin. All patients should be carefully questioned for previous history of penicillin sensitivity. In patients with such a history, even if equivocal, penicillin should not be given. Under such circumstances, erythromycin should be employed in a dose of 250 mg., by mouth four times daily for adults and older children. For small children, a dose of 20 mg. per pound per day, divided into three or four evenly spaced doses, may be used. No dosage should exceed a total of 1 Gm. per day.

*Step I may be omitted if desired.

For Childbirth and Surgical Procedures of the Genitourinary and Lower Intestinal Tract

For childbirth and procedures such as catherization of the bladder, surgery of the genitourinary tract, or surgery of the lower intestinal tract, the following regimen should be employed: *In addition to* either of the penicillin regimens outlined above, streptomycin should be administered in full dosage for five days, with treatment beginning, when possible, two days prior to the surgical procedure. In patients who are sensitive to penicillin chloramphenicol may be substituted.

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NEWS FROM THE AMERICAN HEART ASSOCIATION

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News of the International Society of Cardiology

The Council of the International Society of Cardiology for the term 1958-1962 was elected during the Third World Congress of Cardiology (Brussels, 14-21—September 1958). The new Council is composed as follows:

Honorary Presidents: Dr. Ch. Laubry (France); Dr. P. D. White (U.S.A.).

Executive Committee: President, Dr. I. Chávez (Instituto Nacional de Cardiologia, av. Cuauhtemoc 300, Mexico D. F.): *1st Vice-President,* Dr. D. E. Bedford (33, Devonshire Place, London W. 1., Great Britain); *2nd Vice-President,* Dr. P. W. Duchosal (24, Boulevard des Philosophes, Geneva, Switzerland); *Secretary General,* Dr. V. Puddu (Via Savoia 86, Rome, Italy); *Treasurer,* Dr. L. N. Katz (Michael Reese Hospital, Chicago 16, Ill., U.S.A.)

Members: Dr. A. R. Aixala (Cuba); Dr. E. C. Andrus (U.S.A.); Dr. F. Batlle (Argentine); Dr. G. Biörck (Sweden); Dr. A. Cordeiro (Portugal); Dr. L. V. Décourt (Brazil); Dr. R. Froment (France); Dr. E. T. Gatchalian (Philippines); Dr. F. Herles (Czechoslovakia); Dr. M. Ibrahim (Egypt); Dr. J. D. Keith (Canada); Dr. J. Lequime (Belgium); Dr. J. K. Maddox (Australia); Dr. M. Maekawa (Japan); Dr. K. Matthes (Germany); Dr. M. Nellen (Union of South Africa); Dr. S. Padmavati (India); Dr. F. Rojas V. (Chile); Dr. A. Rotta (Peru); Dr. G. R. Sheikh (Iran).

Committees: The work of the Society is carried out through the activity of the following special committees: *Research Committee:* chairman, Dr. P. D. White; *Social Committee:* chairman, Dr. G. Biörck; *Nomenclature Committee:* chairman, Dr. C. E. Kossmann; *Editorial Committee:* chairman, Dr. P. W. Duchosal; *Committee on Affiliations:* chairman, Dr H. A. Snellen; *Finance-Committee:* chairman Dr. G. Nylin; *Meetings Committee:* chairman Dr. I. Chávez.

Affiliated Societies: Continental Societies: Asian-Pacific, European, Inter-American. *National Societies:* Argentine, Australasia (Australia, New Zealand, Tasmania), Belgium, Brazil, Canada, Chile, Colombia, Cuba, Czechoslovakia, Denmark, Egypt, Eire, Finland, France, Germany, Great Britain, Greece, India, Iran, Israel, Italy, Japan, Mexico, The Netherlands, Pakistan, Peru, Philippines, Poland, Portugal, Puerto-Rico, Spain, Sweden, Switzerland, Union of South Africa, United States of America, Uruguay, Venezuela, Yugoslavia.

Affiliate Funds Supplement National Research Program

Sums totaling nearly $51,000 have been contributed by AHA affiliates and chapters (as of Sept. 21, 1959) to supplement the Association's national research support program for the 1959-60 fiscal year.

In addition to those reported in previous issues of *Circulation,* the following Heart Associations have provided funds for this purpose:

Delaware Heart Association, $2,000: partial support of the grant of William S. Blakemore, M.D., University of Pennsylvania School of Medicine;

Heart Association of Maryland, $5,000, Lower Eastern Shore and Upper Eastern

Shore (Md.) Chapters, $500 and $1,000 respectively for a total of $6,500: partial support of the fellowships of Milton Corn, M.D. and Charles R. Cooke, M.D., both at Johns Hopkins Hospital;

Kansas Heart Association, $4,200: full support of the fellowship of Miriam A. Derks, Ph.D., University of Kansas Medical Center;

Sullivan County (N.Y.) Heart Chapter, $1,500: partial support of the grant of Kurt Hirschorn, M.D., originally awarded to the late Dr. Charles F. Wilkinson, Jr., New York University Post-Graduate Medical School.

International Symposium On "The Blood Platelets"

An International Symposium on "The Blood Platelets," with attendance open by invitation only, has been scheduled for March 17-19, 1960, at Henry Ford Hospital, Detroit.

Subjects tentatively listed for discussion include: *Historical Perspectives of Platelets; Physiological and Biochemical Mechanisms of Platelets in Blood Coagulation;* and *Clot Retraction of Platelets.* Those wishing information on the meeting may write to Dr. Shirley A. Johnson, Chairman, Committee-International Symposium on Platelets, Henry Ford Hospital, Detroit 2, Mich.

Meetings Calendar

February 3-6: American College of Radiology, New Orleans. William C. Stronach, 20 N. Wacker Drive, Chicago 6, Ill.

February 18-20: Central Surgical Association, Chicago. Angus D. McLachlin, Victoria Hospital, London, Ontario, Canada.

March 17-19: International Symposium on "The Blood Platelets," *By invitation only,* Detroit. Shirley A. Johnson, Henry Ford Hospital, Detroit 2, Mich.

March 19-24: American Academy of General Practice, Philadelphia. Mac F. Cahal, Volker Blvd. at Brookside, Kansas City 12, Mo.

March 21-24: Southeastern Surgical Congress, New Orleans. B. T. Beasley, 1032 Hurt Bldg., Atlanta 3, Ga.

March 26-27: American Psychosomatic Society, Montreal. Eric Wittkower, 265 Nassau Road, Roosevelt, N. Y.

March 28-31: Southwestern Surgical Congress, Las Vegas, Mary O'Leary, 1213 Medical Arts Building, Oklahoma City, Okla.

Renew Journal Subscriptions Through Heart Association

Renewals of subscriptions for 1960 of *Circulation* and *Circulation Research,* official journals published by the Association, should be made through the Publishing Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y. Annual subscription rates are: *Circulation* (12 issues) $14 in the U.S. and Canada, $15 elsewhere. *Circulation Research* (6 issues) $9 in the U.S. and Canada, $10 elsewhere. (Special annual rate for full-time research fellows, $7.) Combined subscription to both journals, $21 in the U.S. and Canada, $23 elsewhere.

April 1-3: American Society of Internal Medicine, San Francisco. R. L. Richards, 350 Post Street, San Francisco 8, Calif.

April 3-6: American Surgical Association, White Sulphur Springs, W. Va. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 4-9: American College of Physicians, San Francisco. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

April 11-16: American Association of Anatomists, New York. Louis B. Flexner, University of Pennsylvania Medical School, Philadelphia 4, Pa.

April 11-15: American Physiological Society, Chicago. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D. C.

May 1-2: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Ave., New York 16, N. Y.

May 3-4: Association of American Physicians, Atlantic City. P. B. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 11-13: American Association for Thoracic Surgery, Miami Beach. H. T. Langston, 7730 Carondelet Ave., St. Louis 5, Mo.

May 23-28: American College of Cardiology, Indianapolis. Philip Reichert, 2709 Empire State Bldg., New York 1, N. Y.

June 8-12: American College of Chest Physicians, Miami Beach. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Ill.

June 11: International Cardiovascular Society, North American Chapter, Miami Beach. P. T. DeCamp, 3503 Prytania St., New Orleans 15, La.

Abroad

May 2-11: Pan American Medical Association Congress, Mexico City. Joseph J. Eller, 745 Fifth Avenue, New York 22, N. Y.

May 6-8: International Congress of Phlebology, Chambery, France. J. Marmasse, 3 Rue de la Republique, Orleans, Loiret, France.

May 15-18: International College of Surgeons, International Congress, Rome. Secretariat, 1516 Lake Shore Drive, Chicago 10, Ill.

May 23-28: Asian-Pacific Congress of Cardiology, Melbourne, Australia. A. E. Doyle, Alfred Hospital, Melbourne S. 1, Victoria, Australia.

August 14-20: Inter-American Congress of Cardiology, Rio de Janeiro. Magalhaes Gomes, Av. Nilo Pecanha, 38, Rio de Janeiro, Brazil.

August 24-27: International Congress of Internal Medicine, Basel, Switzerland. Secretariat, 13, Steinentorstre, Basel, Switzerland.

August 28-September 1: International Congress on Diseases of the Chest, Vienna. A. Sattler, American College of Chest Physicians, Frankgasse 8, Vienna, Austria.

September 1-3: First International Congress of Nephrology, Geneva. G. Richet, 149 Rue de Sevres, Paris 15, France.

September 18-25: European Congress of Cardiology, Rome. Secretariat, Clinica Medica, University of Rome, Italy.

1962

Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc 300, Mexico, D. F.

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1. Russek, H.I.: Am. J. Cardiol. *3*:547 (April) 1959.

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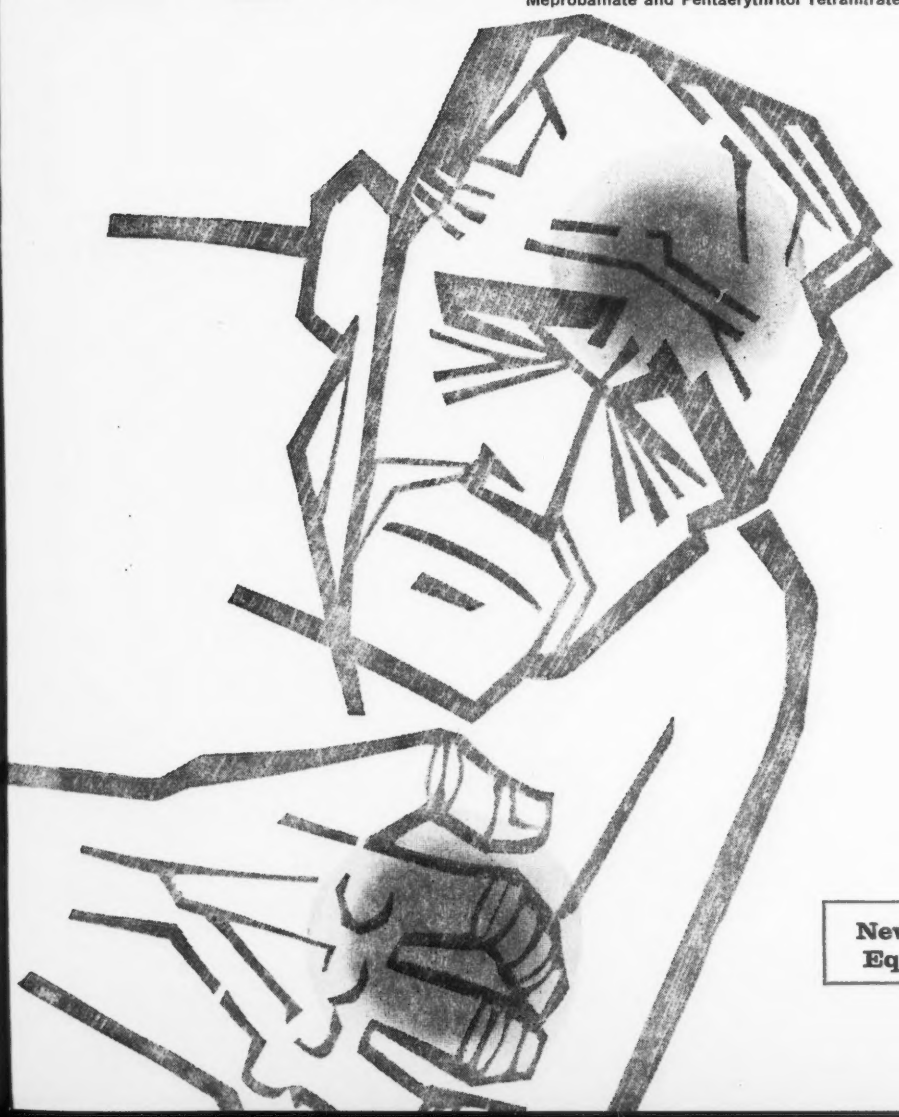

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